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*Review*

# Genomic Alterations in Melanocytic Tumors: A Review of Spitz Tumors, Blue Nevi, Deep Penetrating Melanocytomas and Pigmented Epithelioid Melanocytomas

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**Abstract:** The arena of melanocytic histopathology has experienced tremendous growth in the last decade. The advancement is attributed to incorporating various molecular tests in benign, intermediate, and malignant melanocytic tumors. Most molecular testing has been mainly applied in clinically advanced-stage melanoma to determine the molecular alteration to help guide therapy (e.g., BRAF inhibitors in BRAF mutated melanomas). However, with more availability and, to a certain degree, affordability of certain molecular tests, multiple studies have been conducted on benign/intermediate lesions in an attempt to understand further the driving molecular alterations allowing for the proliferation of certain melanocytic lineages. This review article discusses and illustrates examples of recently recognized entities with their corresponding genomic alterations in the Spitz lineage, blue nevi, deep penetrating melanocytomas, and pigmented epithelioid melanocytomas.

**Keywords:** melanocytic tumors; melanocytic nevi; melanocytomas; genomic alterations



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## 1. Introduction

Molecular alterations have been recognized as pivotal events driving oncogenesis in various neoplasms with biological potential spanning benign and malignant spectrums across different organs and various histogenetic categories. The field of molecular alterations in melanocytic pathology has witnessed tremendous growth in recent years. In the early phase of integrating molecular tests in melanocytic tumors, emphasis was mostly placed on *BRAF* mutations in metastatic melanoma to help provide targeted therapeutic agents. In recent years, the field has expanded drastically in recognizing molecular alterations and fusions corresponding to certain histopathologic features and certain melanocytic subtypes. In this review article, we will list the currently recognized molecular alterations that correspond to specific melanocytic histomorphology. The genomic alterations characterizing Spitz tumors, blue nevi, deep penetrating melanocytomas, and pigmented epithelioid melanocytomas and their corresonding hisotopathologic findings are summarized in Table 1.

**Table 1.** Genomic alterations and corresponding histologic features in Spitz tumors, blue nevi, deep penetrating melanocytomas and pigmented epithelioid melanocytomas.

| Tumor Type | Genomic Alteration | Histologic Findings | Molecular Testing |
|---|---|---|---|
| Spitz tumors | *HRAS* mutations and/or 11p amplifications | Predominantly intradermal with desmoplastic stroma; large melanocytes [1,2] | NGS, FISH, SNP microarray, CGH [3] |
| | *ALK* fusions | Plexiform architecture; non-pigmented melanocytes with pericellular clefts; can show cytologic atypia and increased mitotic activity [4–7] | NGS, FISH [3] |
| | *ROS1* fusions | Prominent junctional melanocytic nests with trans-epidermal elimination and adnexal involvement; sometimes angiomatoid Spitz; can show cytologic atypia [8] | NGS, FISH [3] |
| | *NTRK1* fusions | Thin elongated rete ridges; frequent Kamino bodies; rosette-like structures; extreme maturation; often associated with a lymphocytic infiltrate [4,6,9,10] | NGS, FISH [3] |
| | *NTRK3::MYO5A* fusions | Spindled melanocytes; fascicular to plexiform growth pattern; palisading and rosette-like structures [11] | NGS, FISH [3] |
| | *NTRK3::ETV6* fusions | Epithelioid melanocytes with abundant eosinophilic cytoplasm and distinct cell borders; pleomorphic nuclei; large coalescing nests [7,11] | NGS, FISH [3] |
| | *NTRK3::MYH9* fusions | Large epithelioid melanocytes; syncytial growth with central desmoplastic stroma and peripheral collagen trapping [11] | NGS, FISH [3] |
| | *MET* fusions | Large nests of intermediate to large epithelioid to spindled melanocytes; pericellular clefts; epidermal hyperplasia [12] | NGS, FISH [3] |
| | *RET* fusions | Large nests of small to intermediate-sized, monotonous epithelioid, discohesive melanocytes [13,14] | NGS, FISH [3] |
| | *BRAF* fusions | Superficial cellular sheet-like dermal component; less cellular base with prominent desmoplastic reaction; no maturation; large epithelioid melanocytes; can show severe cytologic atypia; increased mitotic figures [4,9,15–18] | NGS, FISH [3] |
| | *MAP3K8* fusions and mutations | Asymmetric, nodular, or dome-shaped; epidermal hyperplasia; nested junctional component; no maturation; epithelioid melanocytes with large uniform nuclei and prominent nucleoli; multinucleated giant melanocytes; can show severe cytologic atypia; increased mitotic figures; ulceration [7,9,19–23] | NGS, FISH [3] |
| | *MAP2K1* mutations | Wedge-shaped; overlapping features with deep penetrating and dysplastic nevi; plexiform growth pattern; tendency to converge around the adnexal structures and neurovascular bundles; melanin pigment accumulation in stroma and melanophages; poor maturation; large epithelioid melanocytes; can show severe cytologic atypia [21,24–26] | NGS [3] |

**Table 1.** *Cont.*

| Tumor Type | Genomic Alteration | Histologic Findings | Molecular Testing |
| --- | --- | --- | --- |
| Blue nevi | *GNAQ*, *GNA11* or *CYSLTR2* mutations | Intradermal; spindled dendritic pigmented melanocytes and melanophages; sclerotic stroma; a cellular variant with distinct cellular fascicles and nests of plump spindled to oval, clear, or finely pigmented melanocytes; no maturation [27–29] | NGS [3] |
| Melanocytomas of the low cumulative sun damage (CSD) pathway:<br><br>Deep penetrating melanocytoma | *CTNNB1*, *APC*, *MAP2K1*, *BRAF* mutations | Wedge-shaped; predominantly intradermal but can arise in a pre-existing nevus; can extend to the deep dermis and subcutis; fascicular and/or nested growth pattern; heavily pigmented; plump epithelioid to spindled cells; no maturation; can show cytologic atypia; occasional mitotic figures [30–33] | NGS [3] |
| Melanocytomas of the low cumulative sun damage (CSD) pathway:<br><br>Pigmented epithelioid melanocytoma | *PRKAR1A* mutations or *PRKCA* fusions | Nodular or wedge-shaped; epidermal hyperplasia; predominantly intradermal; nested or solid growth pattern; heavily pigmented large multinucleated and small epithelioid, spindled, and dendritic melanocytes and melanophages; no maturation [34–40] | NGS, FISH [3] |

## 2. Spitz Tumors

### *2.1. HRAS-Driven Spitz Tumors*

Genomic studies have found that true Spitz lineage, unlike conventional nevi and melanomas, lack *BRAF*- or *NRAS*-activating mutations and instead often harbor kinase fusions and characteristic *HRAS* mutations and/or amplifications, which have become defining diagnostic criteria in the 2018 WHO classification of skin tumors [41]. *HRAS* is a proto-oncogene located on chromosome 11p that is part of to the *RAS* family of oncogenes and encodes a GTPase, which is a member of the small GTPase family that, upon activation by growth factors, stimulates multiple downstream pathways, namely MAP kinase and PI3K-AKT signaling, to promote cell proliferation and survival [42,43]. *HRAS* mutations with or without 11p amplification define a subtype of Spitz neoplasms with distinctive clinical and morphologic features [44]. Clinically, these lesions tend to be symmetric and raised with a predilection to the head and neck, and extremities [45]. Activating mutations in *HRAS* have also been described in association with grouped patterns of Spitz nevi, especially agminated Spitz nevi, whether arising in a nevus spilus or not [46,47]. Histologically, *HRAS*-mutated Spitz nevi are variably cellular and characteristically show an intradermal component with desmoplastic stroma (Figure 1), particularly when 11p amplification is present [1,2]. Cytologically, cells are typically enlarged with epithelioid or spindle cell morphology and can have vesicular nuclei with ample amphophilic cytoplasms and a low proliferation rate [1,2]. A larger-scale study by Busam et al. of 40 melanocytic tumors with 11p amplification found they are not always necessarily desmoplastic in their growth pattern. They can be non-desmoplastic and papillomatous in appearance and, in some cases, display atypia with deep bulbous growth [45].

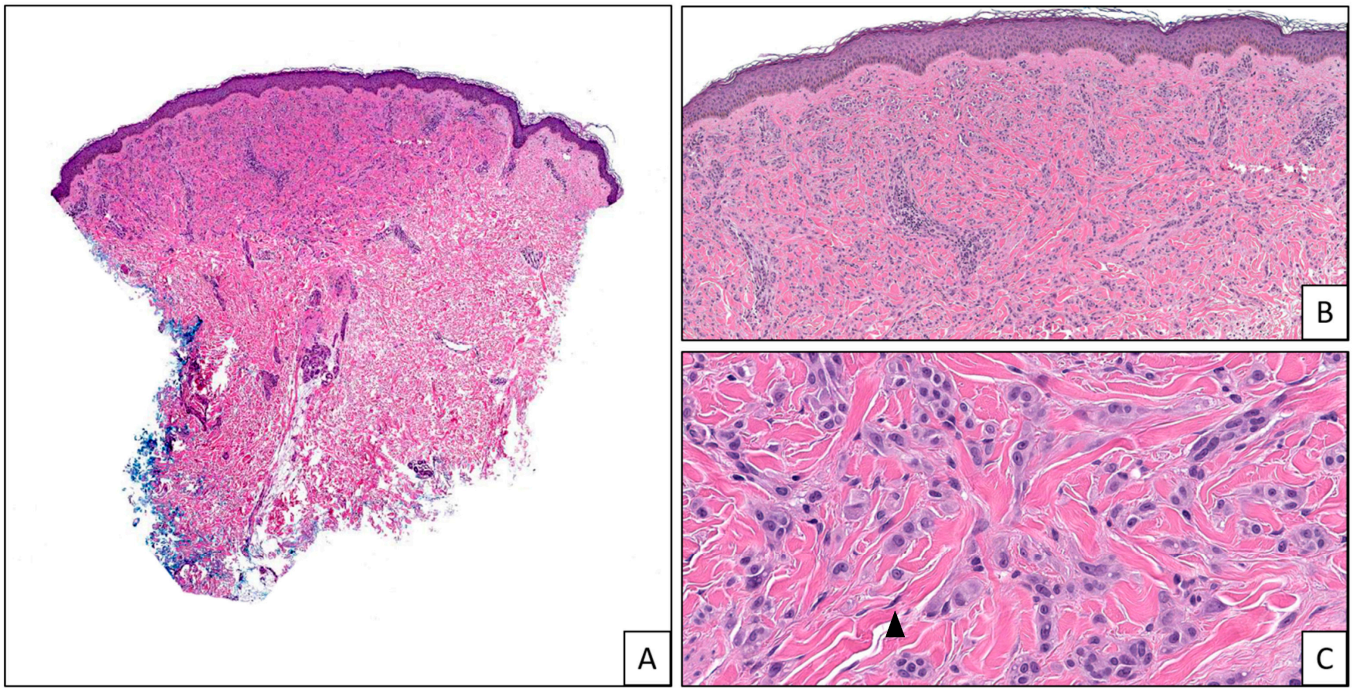


**Figure 1.** Desmoplastic Spitz nevus: (**A**) a dermal-based melanocytic proliferation (2×). (**B**). The melanocytes induce background dermal fibrosis/desmoplasia (4×). (**C**). The melanocytes display a Spitzoid morphology (arrow head) with uniform atypia and no significant pleomorphism or mitotic activity (20×). These nevi are usually driven by HRAS mutations.

Molecular tests commonly used to detect *HRAS* mutations and 11p copy number changes include next-generation sequencing (NGS) or pyrosequencing and single-nucleotide polymorphism (SNP) microarray, fluorescence in situ hybridization (FISH) or comparative genomic hybridization (CGH), respectively [3].

### 2.2. ALK-Fused Spitz Tumors

Tyrosine kinase fusion-associated Spitz neoplasms are an emerging category of tumors with specific phenotypic patterns that can improve the accuracy of identifying a tumor as belonging to the Spitz family. These fusions constitute primary driver events that seem to correlate with specific histologic features of each melanocytic neoplasm.

The anaplastic lymphoma kinase (*ALK*) gene is an oncogene located on chromosome 2p and synthesizes a tyrosine kinase receptor that belongs to the insulin receptor superfamily [48]. Activating genomic alterations in this gene, including fusions with several partner genes, promote cell proliferation by activating MAPK, PI3K, and JAK3 signaling pathways [49,50].

Clinically, *ALK*-fused Spitz neoplasms characteristically present as solitary, large, amelanotic, polypoid lesions on the extremities of young patients [51]. Morphologically, these tumors are commonly dome/wedge-shaped compound lesions with a predominant dermal melanocytic component that can show an infiltrative pattern [4–6]. Cells are typically non-pigmented, spindled with pericellular clefts or mixed with an epithelioid component and frequently show vesicular nuclei with prominent nucleoli and an amphophilic cytoplasm [4–7]. A minor subset of tumors, however, can have worrisome features that include marked cytologic atypia, increased mitoses, and ulceration [4,51,52] (Figure 2). Though non-specific, a hallmark feature of *ALK*-fused Spitz neoplasms is their characteristic architectural growth pattern whereby tumor cells arrange themselves in plexiform intersecting fascicles [4,5,7]. Interestingly, *ALK* fusions also tend to correlate with an angiomatoid Spitz morphology [7].

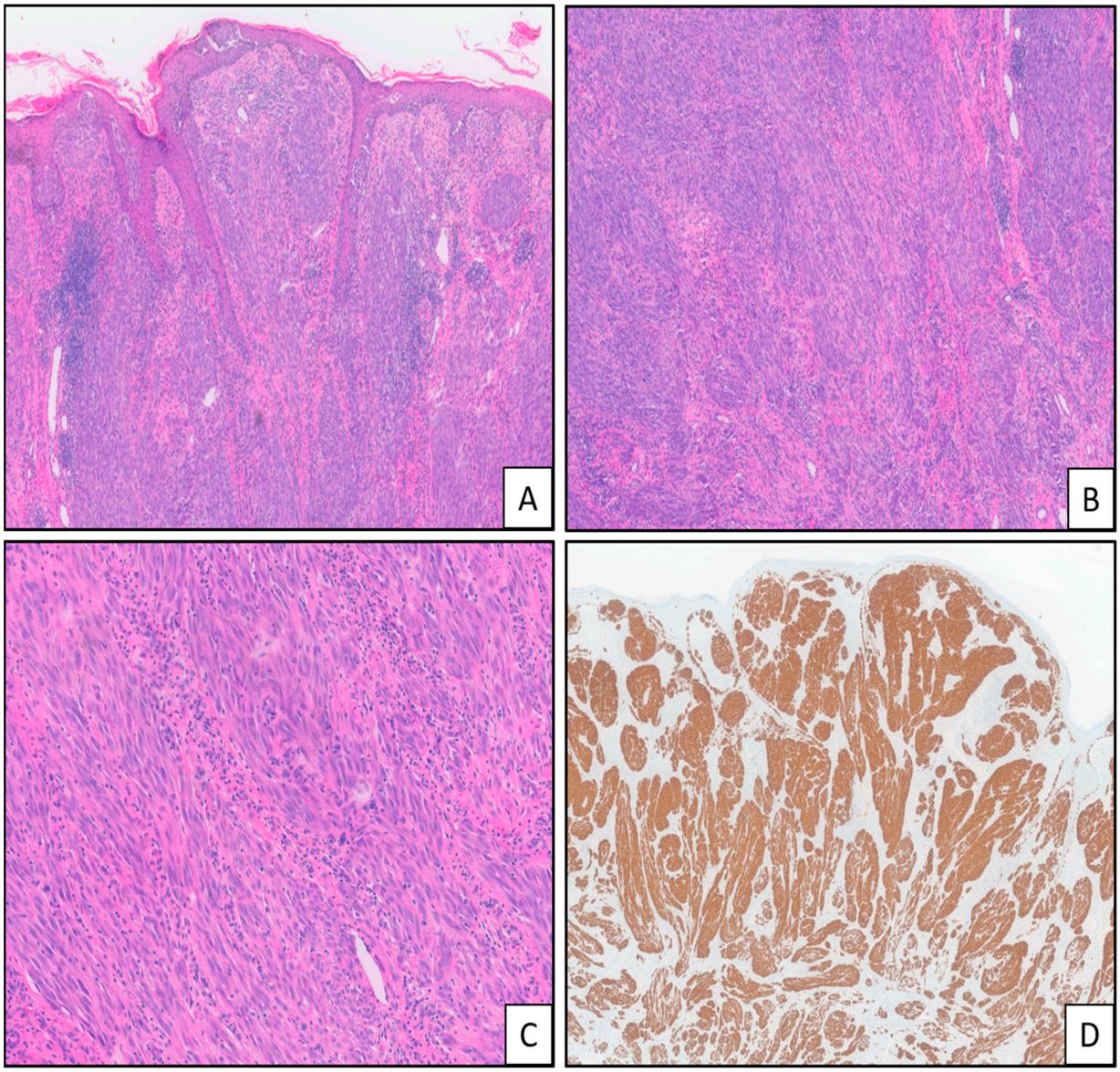


**Figure 2.** ALK-fused Spitz nevus: (**A**). large, amelanotic polypoid melanocytic tumor with irregular growth of junctional melanocytes with multifocal upward migration (2×). (**B**). The melanocytic nests grow in a fascicular and infiltrative pattern (4×). (**C**). The melanocytes show spindled and epithelioid morphology with vesicular nuclei, prominent nucleoli and amphophilic cytoplasm (10×). (**D**). ALK immunostain stains the melanocytes diffusely (2×).

An ALK immunohistochemical stain can act as a surrogate marker to investigate for ALK fusion [51]; however, RNA and DNA-based next-generation sequencing (NGS) strategies and fluorescence in situ hybridization (FISH) with a break-apart probe specific to the *ALK* gene breakpoint region are molecular diagnostic techniques that can be used to test for *ALK* fusions and can potentially investigate the fusion partner [3].

### *2.3. ROS1-Fused Spitz Tumors*

*ROS1* is a proto-oncogene found on chromosome 6q and synthesizes an orphan receptor tyrosine kinase that may activate multiple pathways involved in cell survival and transformation, namely RAS-RAF, JAK3-STAT and PI3K-AKT-mTOR pathways[v] [53]. Ros1 fusion proteins resulting from the fusion of *ROS1* gene with several partner genes frequently lead to constitutive activation of Ros1 signaling and are a relatively common occurrence in Spitz melanocytic tumors [13].

Clinically, *ROS1*-fused Spitz neoplasms are present in young adults as dome-shaped erythematous papules that show a predilection to the lower extremities but can be found all throughout the body [8]. Morphological features are rather non-specific [8]; however, most neoplasms described in the literature show a compound plaque-like to nodular architecture with conspicuous junctional melanocytic nests, trans-epidermal elimination, and occasional involvement of the adnexal epithelium (including acrosyringial units) [7,8,54] (Figure 3). Tumor cells are fairly homogeneous, minimally pigmented, spindled to epithelioid, and show mild to moderate nuclear atypia and low mitotic activity [7,8,54]. Additionally, *ROS1* fusions have also been described in association with desmoplastic, plexiform and angiomatoid Spitz morphologies [8,13].

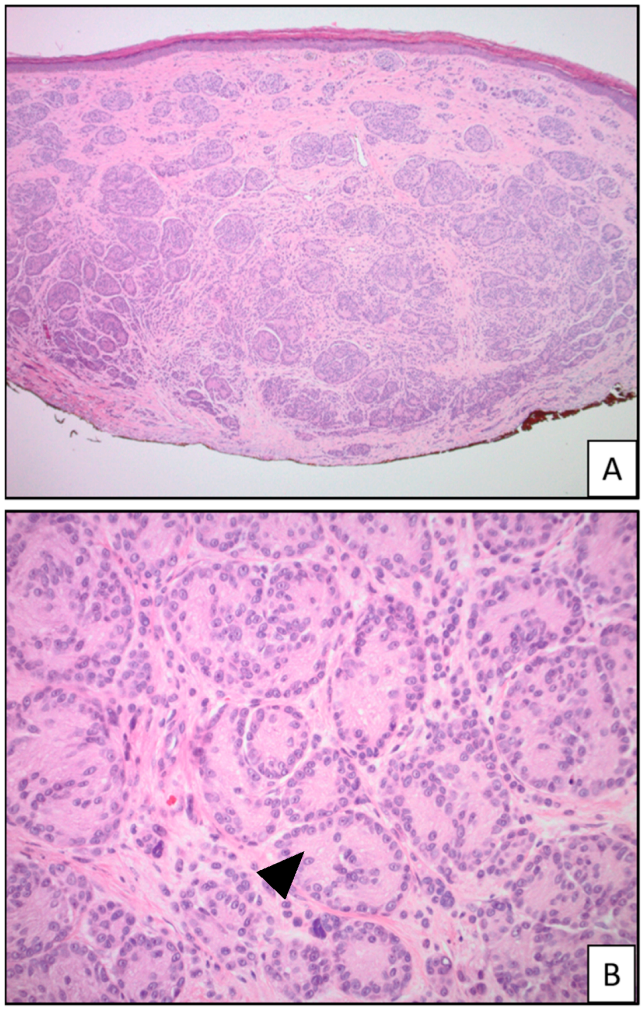


**Figure 3.** NTRK-rearranged Spitz nevus: (**A**). A dermal-based expansile melanocytic proliferation growing in the form of variably sized nests (2×). (**B**). The melanocytic nests are arranged in rosette-like configurations (arrow head) with Spitzoid morphology represented by round eccentric nuclei with uniform atypia and minimal pleomorphism (40×). This tumor molecularly showed *LMNA::NTRK1* fusion.

ROS1 immunohistochemical studies can serve as a surrogate marker; however, from personal experience, the stain is difficult to interpret and, from our experience, has shown significant background uptake of normal cutaneous structures. FISH testing using a break-apart probe labeling the *ROS1* gene or NGS can be applied to identify *ROS1* fusions [3].

### 2.4. NTRK-Fused Spitz Tumors

The neurotrophic receptor tyrosine kinase (*NTRK*) genes *NTRK1*, *NTRK2,* and *NTRK3* are oncogenes that reside on chromosomes 1q, 9q, and 15q, respectively, and encode single-pass receptor tyrosine kinase proteins that belong to the TRK family of tyrosine kinase receptors [55]. Upon binding to neurotrophins, these cell surface receptors can initiate signaling cascades through various mechanisms, including MAPK, PI3K-AKT, and PLCγ1 pathways, leading to cell growth and differentiation [55,56]. Most oncogenic fusions involving the *NTRK* gene family result in chimeric proteins with a retained kinase domain and an acquired dimerizing domain, leading to ligand-independent activation of downstream pathways [57]. *NTRK1*, *NTRK2,* and *NTRK3* fusions have all been reported in Spitz neoplasms, with *NTRK1* being the most common among them [4,7,9–11,57–60]. *NTRK3* fusions were highly prevalent in pigmented spindle cell nevus (also known as spindle cell nevus of Reed) [11,57,59,60].

Spitz tumors with *NTRK1* fusions commonly show a symmetric, compound or intradermal, flat or wedge-shaped architecture and are composed of small spindled to epithelioid melanocytes arranged in lobulated junctional and dermal nests that are organized in a back-to-back pattern forming larger nests [4,9,10]. Characteristically, these lesions show elongated, thin/filigree-like rete ridges, frequent Kamino bodies, rosette-like structures (Figure 3), and extreme maturation and are often associated with a lymphocytic infiltrate [4,6,9,10]. Nuclear pleomorphism is mild to moderate and mitotic figures are rare [6,10].

*NTRK2*-fused Spitz neoplasms are rare. In one case report of an *NTRK2*-fused Spitz nevus, the morphologic features were those of a pigmented spindle cell nevus with essentially large junctional nests of spindled pigmented melanocytes with an abundant eosinophilic cytoplasm, no nuclear atypia and associated hyperplastic epidermis and Kamino bodies [58].

Generally, Spitz tumors with *NTRK3* fusions are compound or intradermal, dome-shaped with associated epidermal hyperplasia [11], but they can have different morphologic patterns depending on the fusion partner gene involved. Lesions with *MYO5A::NTRK3* fusions mainly consist of spindled melanocytes growing in a fascicular to plexiform pattern and show occasional palisading and rosette-like structures [11]. Cases with *ETV6::NTRK3* fusions are mainly composed of large lobulated and coalescing nests of epithelioid melanocytes with an abundant eosinophilic cytoplasm, well-delineated cell borders, and pleomorphic nuclei [7,11]. Lastly, tumors with *MYH9::NTRK3* fusions display syncytial arrangement of large epithelioid melanocytes with peripheral collagen trapping central desmoplastic stromal reactions [11].

Immunohistochemically, pan-TRK immunostain is recommended as a screening test for tumors suspected of harboring NTRK rearrangements. Multiple commercially available antibodies recognize the c-terminal portion of all three TRK proteins. The pan-TRK staining pattern can potentially be predictive of the fusion partners. Cases that harbor NTRK1 or NTRK2 fusions tend to show strong and diffuse cytoplasmic expression. Tumors that harbor NTRK3 fusion tend to have a nuclear expression with or without cytoplasmic staining [61]. Confirmatory molecular diagnostic techniques to identify *NTRK* fusions include FISH with a break-apart probe targeting the specific *NTRK* gene and RNA-based NGS [3].

### 2.5. MET-Fused Spitz Tumors

*MET* is a proto-oncogene found on chromosome 7q that synthesizes a receptor tyrosine kinase that activates MAPK, PI3K-AKT, PLCγ1, β-catenin, and STAT pathways to promote cell proliferation and motility [62]. The number of cases of MET-fused Spitz neoplasms in the literature is limited; however, all the cases reported thus far harbored a breakpoint in intron 14 of the *MET* gene, which contains the regulatory domain of the Met protein and is located upstream of the kinase domain, which is preserved in the fusion protein [63]. At present, there are no distinctive histologic features associated with Spitz neoplasms harboring *MET* fusions. Nevertheless, most cases described are dome-shaped symmetric

lesions showing a compound or intradermal melanocytic proliferation of spindled to epitheliod cells arranged in large nests with pericellular clefting and associated epidermal hyperplasia [12]. NGS and FISH techniques can be used to confirm the presence of *MET* fusions [3].

### 2.6. RET-Fused Spitz Tumors

*RET* is a proto-oncogene that resides on chromosome 10q and encodes a receptor tyrosine kinase that can activate MAPK, PI3K-AKT, and PLCγ1 signaling pathways, thereby regulating cell growth and differentiation [64,65]. *RET* fusions with several partner genes have been reported in a minor subset of Spitz melanocytic neoplasms [13,14]. Spitz neoplasms with RET fusions are not currently associated with specific morphological features. The reported cases are often well-circumscribed, symmetric, plaque-like compound proliferations containing large expansile discohesive nests of small to intermediate-sized, monotonous, epithelioid melanocytes with mild to moderate cytologic atypia [13,14]. *RET* fusions can be detected using NGS or FISH molecular testing [3].

### 2.7. BRAF-Fused Spitz Tumors

Spitz neoplasms with serine/threonine kinase fusions or mutations are a subtype of tumors characterized by worrisome histologic features, higher grade cytologic atypia and a greater likelihood of being classified as atypical Spitz tumor (AST) or malignant Spitz tumor (MST) [4,9,15–18,63,66,67].

*BRAF* is a proto-oncogene located on chromosome 7q that encodes Braf protein, a member of the Raf family of serine/threonine protein kinases, which signals through the MAK kinase pathway to regulate cell proliferation and cell growth [68,69]. Most pathogenic *BRAF* fusions lead to the loss of the N-terminal regulatory/autoinhibitory domains of the Braf protein resulting in autophosphorylation and constitutive activation of the C-terminal kinase domain and MAPK signaling [15,70].

Clinically, Spitz neoplasms with *BRAF* fusions most commonly present in young females as pink papules on the extremities [16]. Morphologically, these lesions can be compound or intradermal with variable plaque-like, wedge-shaped, or nodular configurations and are mostly composed of large epithelioid melanocytes with an abundant amphophilic cytoplasm, vesicular pleomorphic nuclei and prominent nucleoli [4,9,15–18]. Cytologic atypia is frequently moderate to severe, and high mitotic activity is usually evident [4,9,15–18]. Among the different fusion subtypes of Spitz tumors, *BRAF* and *MAP3K8* notoriously show the most prominent cytologic atypia. Characteristically, *BRAF*-fused Spitz tumors have often been described as having a superficial cellular sheet-like dermal component with a less cellular base showing a prominent desmoplastic reaction and lack of melanocytic maturation [4,16,17]. NGS or FISH analysis can both be used to detect *BRAF* fusions [3].

### 2.8. MAP3K8-Mutated Spitz Tumors

The mitogen-activated protein kinase kinase kinase 8 (*MAP3K8*) gene is located on chromosome 10p. It encodes a serine/threonine and tyrosine kinase that is primarily expressed by the immune system and is activated by TNF-alpha, IL1R, and toll-like receptors to promote signaling through activation of the RAF-MEK1/2-ERK1/2 pathway [71–73]. Several *MAP3K8* oncogenic fusions and truncations have been described in Spitz tumors [9,19–23], which commonly result in the loss of the C-terminal inhibitory/regulatory domain of the protein and subsequent unopposed activation of the N-terminal kinase domain leading to increased MEK1/2-ERK1/2 signaling [74,75].

Clinically, *MAP3K8*-fused Spitz neoplasms usually present as pigmented exophytic lesions on the lower extremities of patients of all ages, with a slight female predilection [20,22]. Morphologically, most of these lesions are nodular or dome-shaped, asymmetric with overlying epidermal hyperplasia, and show a compound melanocytic proliferation with a predominantly nested junctional component [7,9,19–23]. Melanocytes are invariably epithelioid with large, uniform nuclei, prominent nucleoli and an abundant eosinophilic

cytoplasm [7,20,23]. Moderate to severe cytologic atypia, deep mitotic figures, absent maturation, scattered multinucleated giant melanocytes, epidermal ulceration, and high-level Pagetoid scatter of melanocytes in the epidermis are frequently reported [7,20,23]. Interestingly, *MAP3K8*-fused Spitz neoplasms frequently harbor additional genomic alterations with prognostic implications, namely biallelic inactivation or deletion of *CDKN2A/B* [7,9,19–21]. *MAP3K8* fusions can be detected using RNA or DNA-based NGS and/or FISH analysis [3].

### 2.9. MAP2K1 Mutated Spitz Tumors

Mitogen-activated protein kinase kinase 1 (*MAP2K1*) is a proto-oncogene that resides on chromosome 15q. It encodes MEK1, a serine-threonine kinase downstream of RAF in the RAS-RAF-MEK-ERK pathway, which in turn activates the MAPK pathway in cell proliferation and differentiation [21,76]. Although rare, *MAP2K1* mutations, particularly in-frame deletions in exons 2 and 3, have been reported in Spitz neoplasms [24]. These deletions frequently lead to the inactivation of the autoinhibitory domain of the MEK1 protein resulting in unopposed activation of the kinase domain [24].

Clinically, *MAP2K1*-mutated Spitz neoplasms are mostly present on the lower extremities of young females as small, pigmented, flat, or mildly elevated lesions [21,24–26]. No distinctive histomorphological features have been established for these lesions given the small number of cases. However, recurring histologic characteristics among the cases described include a wedge-shaped compound or intradermal melanocytic proliferation composed of large epithelioid cells with vesicular nuclei and moderate to severe nuclear pleomorphism arranged in nests and showing a plexiform growth pattern, poor maturation and a tendency to converge around the adnexal structures and neurovascular bundles [21,24–26]. Typically, marked accumulation of melanin pigment and melanophages in the stroma and an absence of epidermal hyperplasia are evident [24,25]. Some cases can also show overlapping features between Spitz nevi and deep penetrating nevi [76] or even dysplastic spitz nevi, also termed SPARK nevi [25]. The morphologic heterogeneity seen in *MAP2K1*-mutated Spitz neoplasms is thought to be related to the prevalence of additional secondary genetic alterations in these tumors [24]. NGS can be reliably used to detect *MAP2K1* mutations [3].

## 3. Blue Nevi

Blue nevi are associated with activating mutations in the Gαq pathway, namely point mutations in GNAQ or *GNA11* and less commonly hotspot mutations in *CYSLTR2* or fusions of protein kinase C (*PKC*) isoforms [77–80]. *GNAQ* and *GNA11* are oncogenes located on chromosomes 9q and 19p, respectively, and encode G protein subunits alpha q and alpha 11 consecutively, which are guanine-binding proteins (G proteins) that are activated upon ligand binding to G-protein-associated receptors and function in downstream signaling [81]. *GNAQ* and *GNA11* hotspot mutations alter intrinsic GTPase activity, leading to constitutive pathway activation [81–83].

Clinically, blue nevi typically present as grayish blue-black macules, papules, or nodules on the head, buttock, or lower extremities and are more frequent in young adult females. The blue color is caused by the Tyndall effect, where light preferentially scatters shorter wavelengths by the melanin in the dermis [84–86]. Histologically, multiple variants are present; however, in all cases, these tumors are almost always intradermal and are characterized by bipolar spindle dendritic pigmented melanocytes and melanophages, often growing in between sclerotic collagen bundles [27]. The cellular variant is usually biphasic and contains distinct cellular areas of plump, spindled to oval melanocytes with clear or finely pigmented melanocytes arranged in fascicles and nests [27,28] (Figure 4). Blue nevi typically show a lack of maturation with descent [27–29].

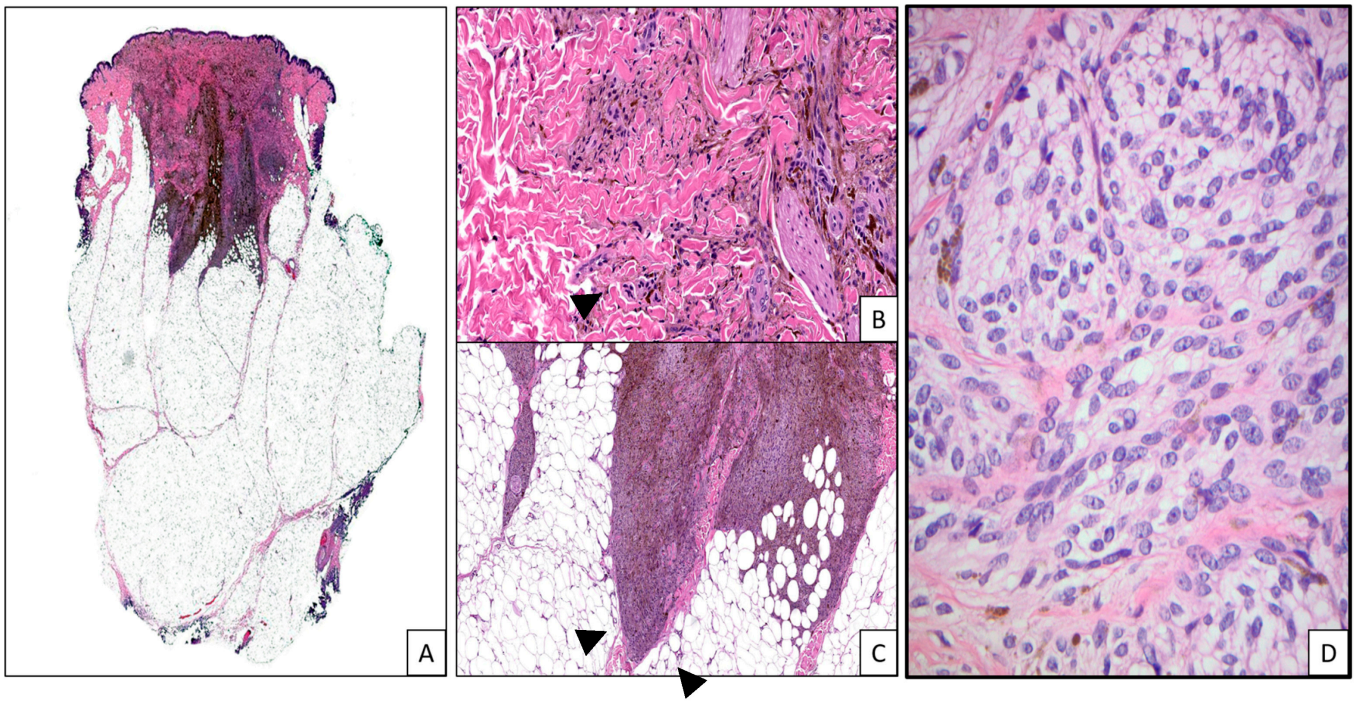


**Figure 4.** Cellular blue nevus: (**A**). A dermal-based melanocytic proliferation with extension into the underlying subcutaneous tissue (1×). (**B**). At the periphery, the melanocytes grow with classic blue nevus features with dendritic shaped melanocytes (arrow head). The melanocytes induce background dermal fibrosis/desmoplasia (4×). (**C**). The deep aspect shows bulbous growth (arrow heads) with well-demarcated borders (4×). (**D**). Cellular areas with epithelioid to spindled melanocytes with uniform atypia, indistinct cell borders, melanin pigment deposition. Cytologically, there is minimal pleomorphism and rare mitoses (40×). Blue nevi commonly harbor *GNAQ* and *GNA11*.

Given the classic histopathologic appearance, most blue nevi do not require molecular testing. If needed, NGS can detect GNAQ and GNA11 point mutations belonging to the blue nevus family lineage [3].

## 4. Deep Penetrating Melanocytoma (DPM)

Deep penetrating melanocytomas (DPMs) are of the low cumulative sun damage (CSD) pathways that, in addition to activating mutations in *BRAF* or *MAP2K1*, harbor mutations that result in constitutive activation of the Wnt/β-catenin pathway, most often point mutations in catenin beta 1 (*CTNNB1*) gene on chromosome 3p, a component of the cadherin-based adherens junction, which prevent its degradation, but alternatively biallelic inactivation of adenomatous polyposis coli (*APC*) gene on chromosome 5q, a major component of the *CTNNB1* degradation complex [87–89]. *CTNNB1* imbalance is implicated in tumor growth, progression, and survival advantage [90].

Clinically, DPNs present in young to middle-aged patients as pigmented papules or nodules, usually on the face, neck, or shoulder [30–32]. Histologically, these lesions can arise in a pre-existing compound nevus. They are characterized by a wedge-shaped silhouette, an inconspicuous junctional component, and a cellular dermal component that can extend to the reticular dermis or even subcutis [30–33]. Melanocytes are commonly arranged in fascicles or nests and typically show heavy pigmentation and a plump epithelioid to spindle cell morphology with a lack of maturation [30–33]. Mild cytologic atypia, nuclear pleomorphism, and occasional dermal mitotic figures are not uncommon [30–33] (Figure 5).

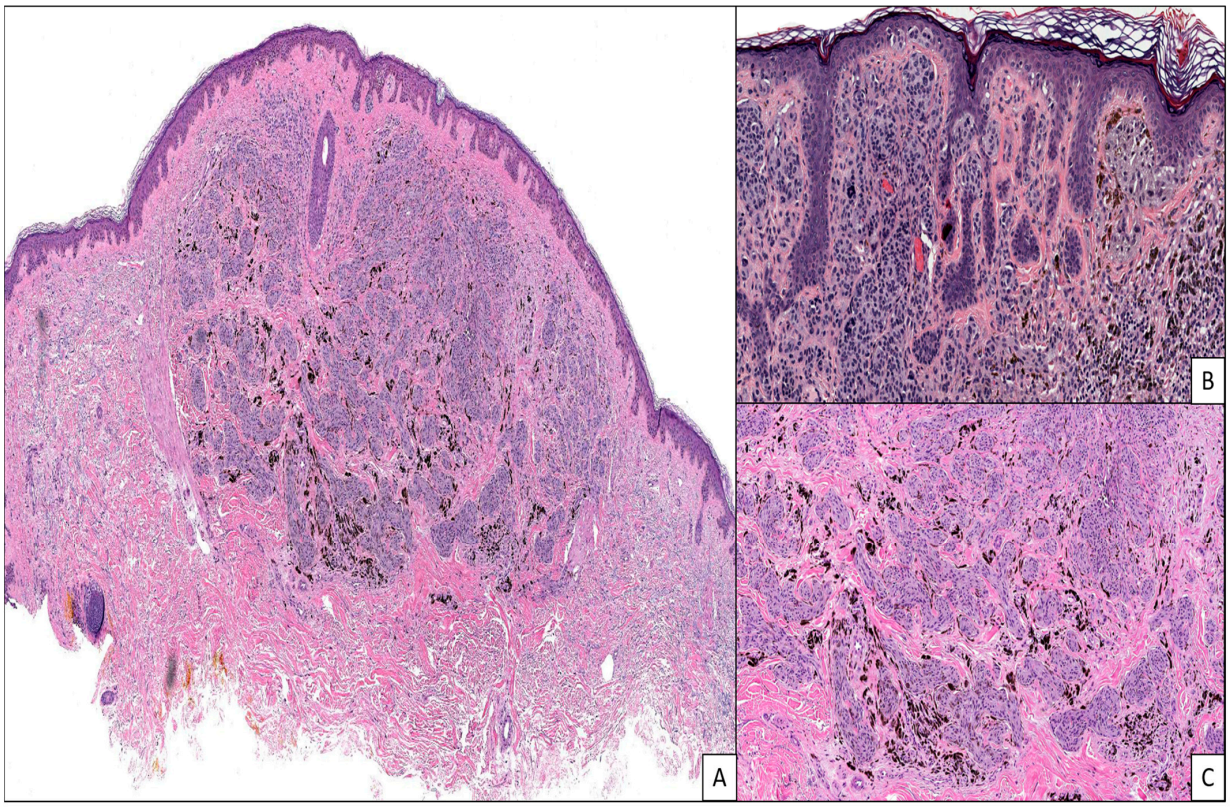


**Figure 5.** Deep penetrating melanocytoma: (**A**). low power demonstrates a compound melanocytic proliferation with two distinct cytomorphologies (1×). (**B**). The first is that of a regular compound nevus with the melanocytes showing maturation with descent and minimal cytologic atypia (10×). (**C**). The second population extends deeper and grows in a plexiform pattern with scattered pigmented macrophages. The cells in the second population show uniform atypia with no significant mitotic activity (10×). Molecular alterations are secondary to MAP kinase activation and β-catenin signaling.

*CTNNB1* and *APC* mutations may be detected using DNA-based NGS [3]. The immunohistochemical stain Beta-catenin can act as a screening tool and a possible marker for *CTNNB1*; it is important to note that the expression of Beta-catenin is in a nuclear pattern and should be seen in the deeper dermal melanocytes, excluding subepidermal nests located immediately underneath the epidermis [91].

## 5. Pigmented Epithelioid Melanocytoma (PEM)

Pigmented epithelioid melanocytomas (PEM) are intermediate-grade melanocytic tumors of the low-CSD pathway that can harbor either biallelic inactivation of the protein kinase cAMP-dependent type I regulatory subunit alpha (*PRKAR1A*) gene on chromosome 17q, a major component of protein kinase A (PKA), which mediates cAMP-dependent signaling and regulates PKA activation, or fusions in the protein kinase C alpha (*PRKCA*) gene, a member of the protein kinase C (PKC) family of serine/threonine kinases, which is involved in a number of essential cellular processes including proliferation, differentiation, survival, and migration [34–39,92–94].

Clinically, PEM is classically present as pigmented, blue to blue-black, dome-shaped, papular or nodular lesions, mostly on the extremities, head and neck, and trunk of young adults, children, and infants [38–40]. Histologically, these lesions typically show a nodular or wedge-shaped proliferation of heavily pigmented large multinucleated and small epithelioid, spindled, and dendritic melanocytes and melanophages with the majority having overlying epidermal hyperplasia [34,36,38–40]. The junctional component is usually inconspicuous, and the dermal component characteristically consists of melanocytes with large vesicular nuclei and prominent nucleoli arranged in single cells and small nests that

show a lack of maturation [34,36,38–40] (Figure 6). PEMs with *PRKAR1A* mutation are associated with cytologic heterogeneity and may have conventional nevus components with smaller nests, separated by fibrous bands of collagen [35,37–40], while those with *PRKCA* fusions tend to show solid sheets of pigmented epithelioid melanocytes [35,36,39].

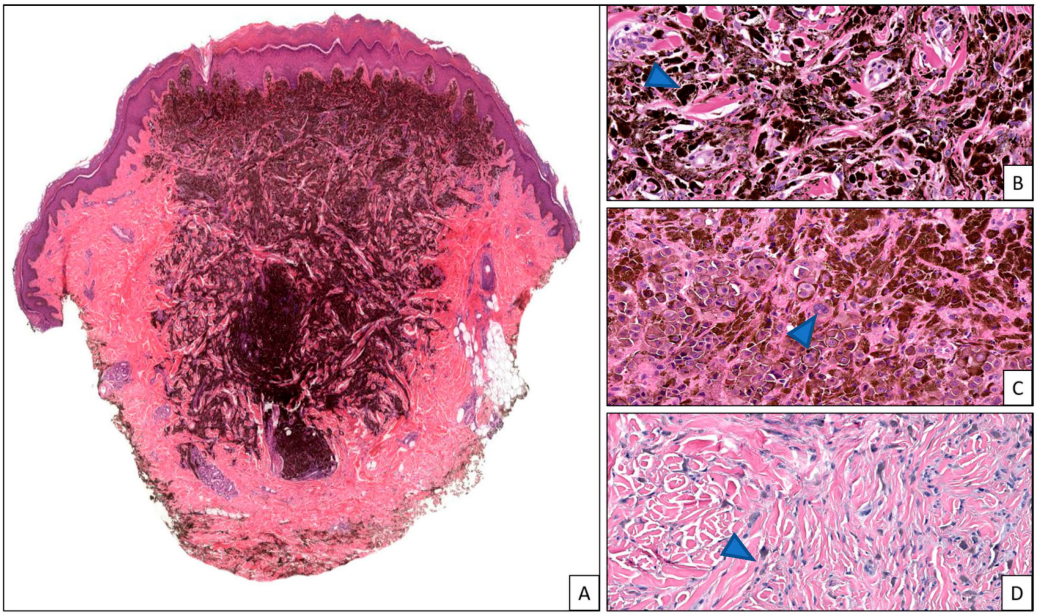


**Figure 6.** Pigmented epithelioid melanocytoma: (**A**). heavily pigmented melanocytic proliferation with overlying epidermal hyperplasia (1×). (**B**–**D**). The lesion consists of three cell types. (**B**). Heavily pigmented melanophages (blue arrow head) (20×). (**C**). Epithelioid melanocytes (blue arrow head) (20×). (**D**). Dendritic melanocytes with vesicular chromatin and prominent nucleoli (blue arrow head) (20×).

RNA and DNA-based NGS and FISH with a break-apart probe specific to the PRKCA gene can be used to identify *PRKAR1A* mutations and *PRKCA* fusions [3].

## 6. Conclusions

Significant advances in tumor genomics have provided insight into the biology and proliferation of melanocytic tumors. Integration of clinical, histological, immunohistochemical and molecular alterations has given rise to better identification of certain melanocytic proliferations that were most likely previously lumped in the "uncertain biologic potential" category. Separating melanocytic neoplasms based on the reproducible genetic alterations and clinical phenotypes has improved our understanding of these neoplasms, facilitating future research and clinical personalized management.

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