

Solid Tumour Section

Review

Skin: Spitz tumors

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Published in Atlas Database: July 2012

Online updated version : <http://AtlasGeneticsOncology.org/Tumors/SpitzTumorID6241.html>
DOI: 10.4267/2042/48473

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Classification

Note

Neoplasms arising from melanocytes in the skin may be benign, in which case they are termed "nevi", or malignant, in which case they are termed "melanomas". There are several variants of cutaneous melanocytic tumors, characterized by differing clinical and pathologic features. Spitz tumors include a group of cutaneous melanocytic tumors that share certain histologic features. Spitz tumors may be classified as Spitz nevi [which are benign], spitzoid melanomas [which are malignant], and "atypical Spitz tumor" [a group of tumors whose biologic behavior cannot be accurately predicted on the basis of their histopathologic features] (Barnhill, 2006a; Barnhill, 2006b). Spitz nevi show characteristic cytologic and architectural features, described below. Only some of these characteristics are seen in atypical Spitz tumors and spitzoid melanomas.

Clinics and pathology

Note

The diagnosis of Spitz tumors may be suspected on clinical grounds, as these tumors can have distinctive clinical appearances. Characteristic clinical features include onset during childhood, small (The histopathologic evaluation of melanocytic tumors of the skin relies on assessment of several architectural and cytologic features, some of which are characteristic of nevi, while others are of melanomas. Spitz tumors

are a unique subtype of melanocytic tumors in that tumors at the benign end of the spectrum [Spitz nevi] still commonly exhibit morphologic features that are often seen in melanomas. These include cytologic characteristics such as large cell size, abundant cytoplasm, large, often vesicular, nuclei, intranuclear pseudoinclusions and sometimes prominent nucleoli; this constellation of cytologic features is often referred to as "spitzoid". Other features include lack of pigmentation (with the exception of the "pigmented spindle cell nevus", thought to be a Spitz nevus variant), peripheral circumscription (cell aggregates rather than single cells mark the periphery of the epidermal component), symmetry, clefts around cells and aggregates of cells (particularly at the dermo-epidermal junction), so-called Kamino bodies (basement membrane-like material found in the superficial dermis), epidermal changes (thickening and hypergranulosis), "maturation" of any dermal component (the cells tend to get smaller with less cytoplasm in the deeper dermal portion) and single cell dispersion at the base of the lesion. Spitz nevi can also have an increased number of mitotic figures, consistent with their comparatively rapid, but ultimately self-limited, growth.

In 1948, Sophie Spitz originally described an unusual melanocytic tumor that occurred in children and was characterized by distinctive cytoarchitectural features, many of which were thought to be unique to melanoma. Spitz therefore termed these tumors "juvenile melanomas" (Spitz, 1948).



Figure 1. Spitz nevus on the right cheek of a young girl. The tumor is small, symmetrical, and dome-shaped, and lacks pigmentation.

In subsequent years, with the realization that the majority of these tumors followed a benign course (Allen and Spitz, 1953), they were designated "Spitz nevi".

Since that time, pathologists have identified spitzoid cytologic features in melanocytic tumors that lack the classical diagnostic criteria for Spitz nevi. Some of these tumors show sufficient cytologic atypia and mitotic activity to merit classification as melanoma ["spitzoid melanoma"] and behave clinically in a malignant fashion (development of distant metastasis and patient death). These spitzoid melanomas include melanomas that arise from pre-existing Spitz nevi as well as melanomas with spitzoid morphologic features that arise de novo, without an antecedent Spitz nevus (Kamino, 2009). Other Spitz tumors show greater degrees of cytologic atypia and mitotic activity than permissible for nevi, but falling short of that required for a definite diagnosis of melanoma. Several studies have shown that in such tumors, correlation of histopathologic features with clinical outcomes is poor, and therefore they have been designated "atypical Spitz tumors of uncertain malignant potential" [or simply "atypical Spitz tumors"] to reflect the uncertainty regarding their likely clinical behavior. Part of the difficulty arises because there is not a single histological feature that in isolation defines either a Spitz nevus or a melanoma. Rather, a credible pathologic diagnosis of a melanocytic tumor requires assessment and consideration of a range of architectural and cytologic features as well as correlation with clinical data including the age of the patient and site of the lesion.

Given the aforementioned considerations, it is perhaps not surprising that the histologic grading of Spitz

tumors as benign [Spitz nevi], malignant [spitzoid melanoma] or tumors of intermediate/uncertain malignant potential [AST] is poorly reproducible between pathologists, even among experts in melanocytic tumor pathology (Barnhill et al., 1999; Cerroni et al., 2010). ASTs in particular constitute a heterogeneous group of tumors with imperfectly defined diagnostic criteria. Therefore, there is a need for better genetic and molecular characterization of Spitz tumors, along with genotype-phenotype correlations, in order to improve the precision of their classification and also to more accurately predict their biologic behavior. Recent discoveries of genetic subsets of Spitz tumors are described below.

Disease

Spitz nevus

Epidemiology

Usually in fair-skinned individuals. May be seen at any age, but are commonest in children and young adults. Between half and two-thirds of cases occur in the first two decades (Lyon, 2010).

Clinics

Spitz nevi present as single, dome-shaped papule or nodule typically <6mm in diameter. Most often, they occur on the face but can occur at any cutaneous location. Commonly, they are not pigmented, but may have a pink to reddish color. Some lesions are heavily pigmented, but those typically fall under the category of pigmented spindle cell nevus (Ferrara et al., 2005; Mooi, 2002). Unusual clinical presentations include grouped/agminated Spitz nevi (Herd et al., 1994; Krasovec et al., 1995) or disseminated Spitz nevi (Rim

et al., 2002; Smith et al., 1986), which may develop abruptly [eruptive Spitz nevi] (Gantner et al., 2011; Levy et al., 2007).

Pathology

Spitz nevi usually involve both the epidermis and dermis (i.e. compound Spitz nevi), although occasionally they may be located entirely at the epidermal-dermal junction (junctional Spitz nevi) or within the dermis (intradermal). They are symmetrical, well-circumscribed and wedge-shaped, and are composed of clusters (nests) and bundles (fascicles) of melanocytes at the dermo-epidermal junction and/or in the dermis. Artifacts clefts are common around intraepidermal nests, and there is epidermal hyperplasia and prominence of the epidermal granular layer. Eosinophilic (Kamino) bodies may be seen in the

superficial dermis. The melanocytes are epithelioid and/or spindle-shaped, and contain moderate to large amounts of amphophilic or ground-glass cytoplasm. They rarely contain cytoplasmic melanin.

Their nuclei are relatively large, round to oval in shape, and show mild pleomorphism with mostly small, round, regular nucleoli.

Maturation (decrease in nuclear size of melanocytes with chromatin becoming darker accompanied by reduction in the amount of cytoplasm) with depth is present in many cases (Requena et al., 2009). Occasional mitotic figures may be seen, but are usually located in the superficial dermal component; deep mitoses and atypical mitotic figures are not seen in Spitz nevi (Barnhill, 2006; Crotty, 1997; Lyon, 2010; Mooi, 2002; Walsh et al., 1998).

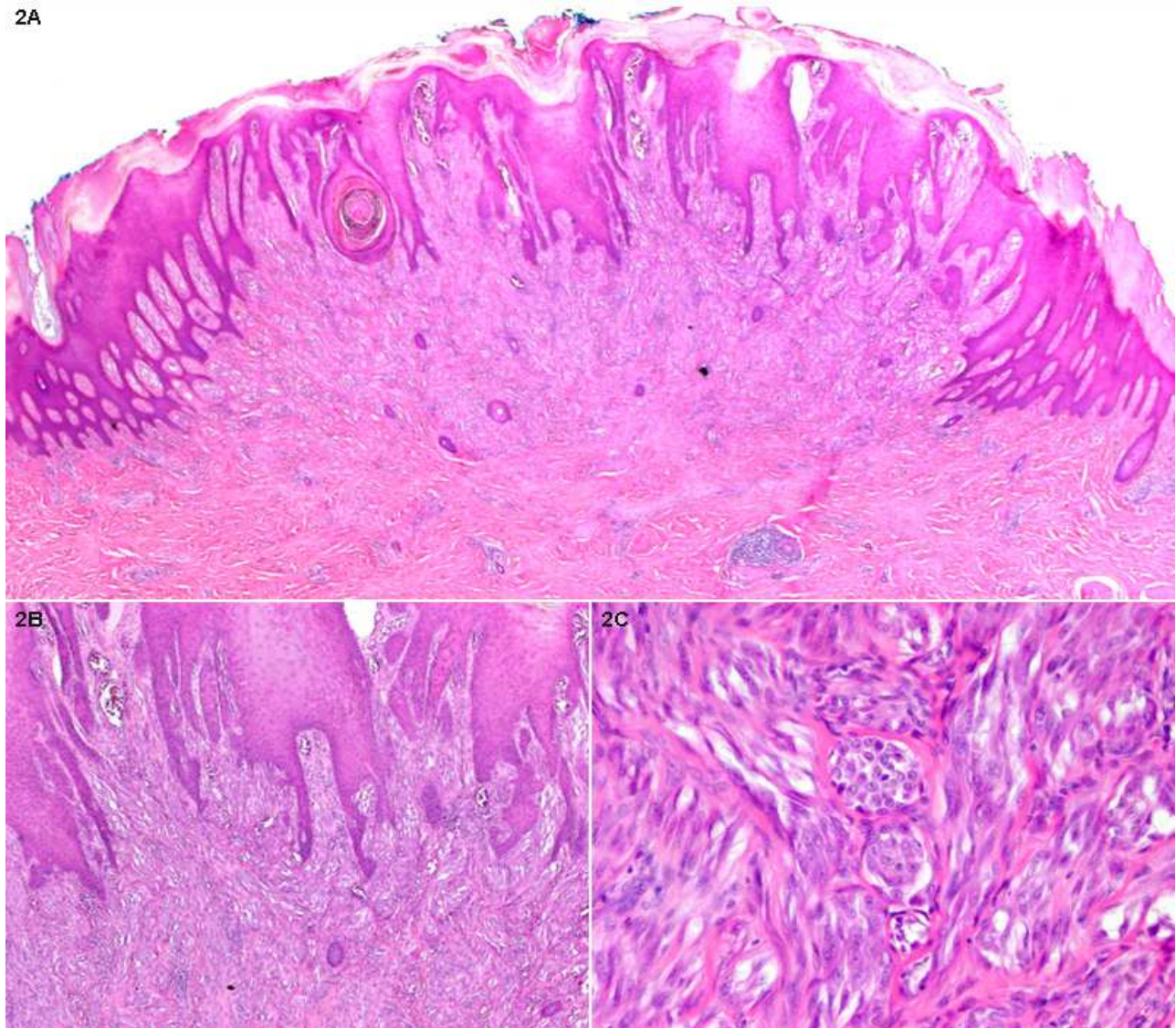


Figure 2. Compound Spitz nevus from right calf of 24 year old male. 2A) Symmetrical, compound lesion associated with epidermal hyperplasia. 2B-C) Lesion is composed of fascicles and nests of epithelioid and spindle-shaped melanocytes with moderate amounts of amphophilic cytoplasm. Mitotic activity is infrequent.

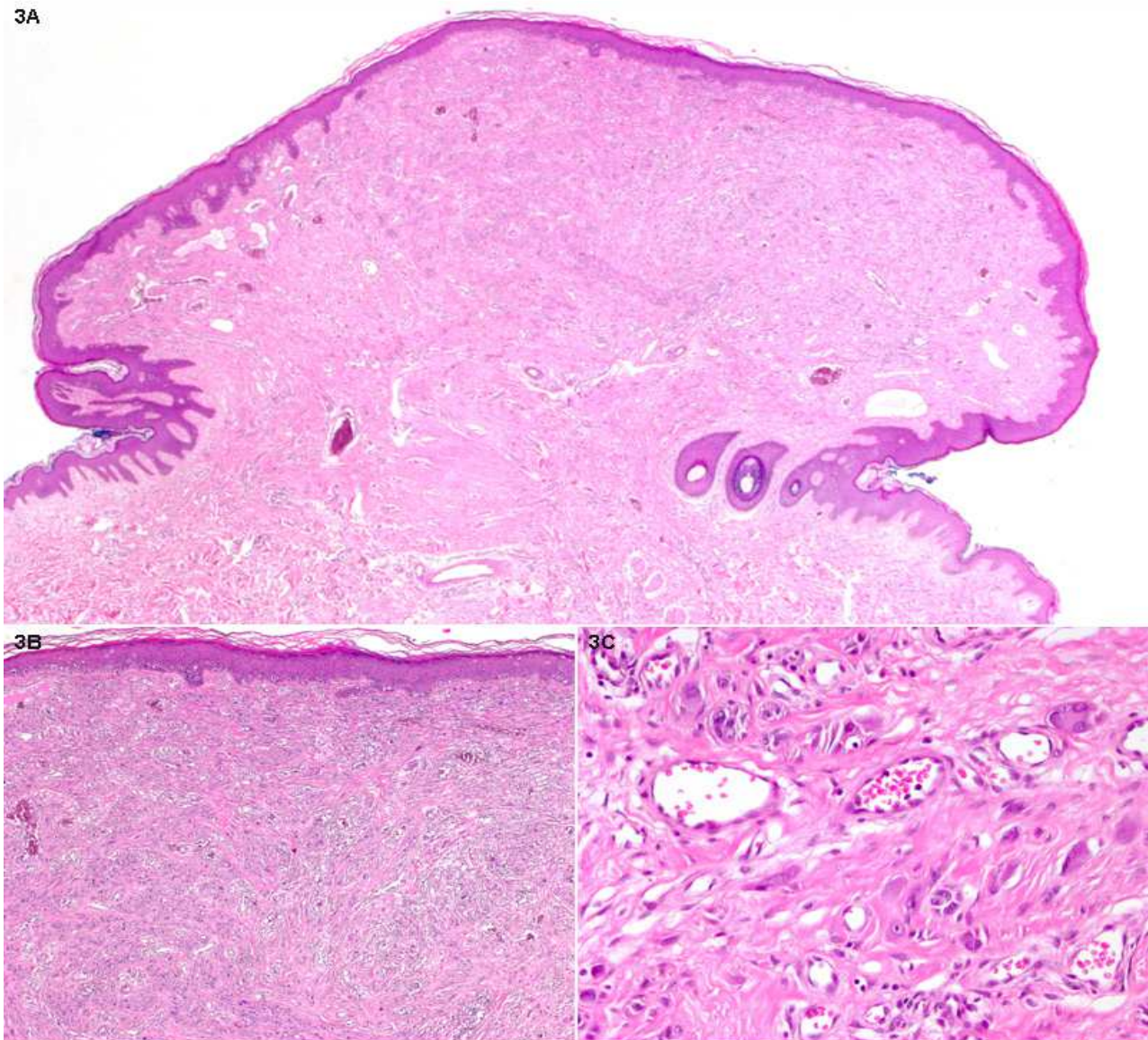


Figure 3. Desmoplastic/sclerosing Spitz nevus from right thigh of 30 year old male. 3A) Polypoid, relatively symmetrical tumor. 3B-3C) Lesion is composed of large epithelioid and oval cells admixed with abundant collagenous stroma.

Pagetoid intraepidermal scatter of single melanocytes or nests of melanocytes (a feature often also present in melanomas) in the central portion of the lesion is not uncommon.

Combined melanocytic nevi, comprising a Spitz nevus component in conjunction with another nevus type [usually acquired nevi] are not uncommon (Scolyer et al., 2004). Less common are histologic variants such as desmoplastic/sclerosing, angiomatoid, myxoid and plexiform Spitz nevi (Lyon, 2010), and pigmented spindle cell nevus (Ferrara et al., 2005; Mooi, 2002).

Treatment

Complete excision.

Evolution

No recurrence if completely excised. May infrequently recur if incompletely excised.

Prognosis

Benign.

Disease

Atypical Spitz Tumor (AST)

Epidemiology

May present at any age, although they are frequently diagnosed in the first two decades.

Clinics

Clinically, ASTs may show some features in common with Spitz nevi, although they exhibit one or more worrisome characteristics, such as large size, variable pigmentation, asymmetry or ulceration.

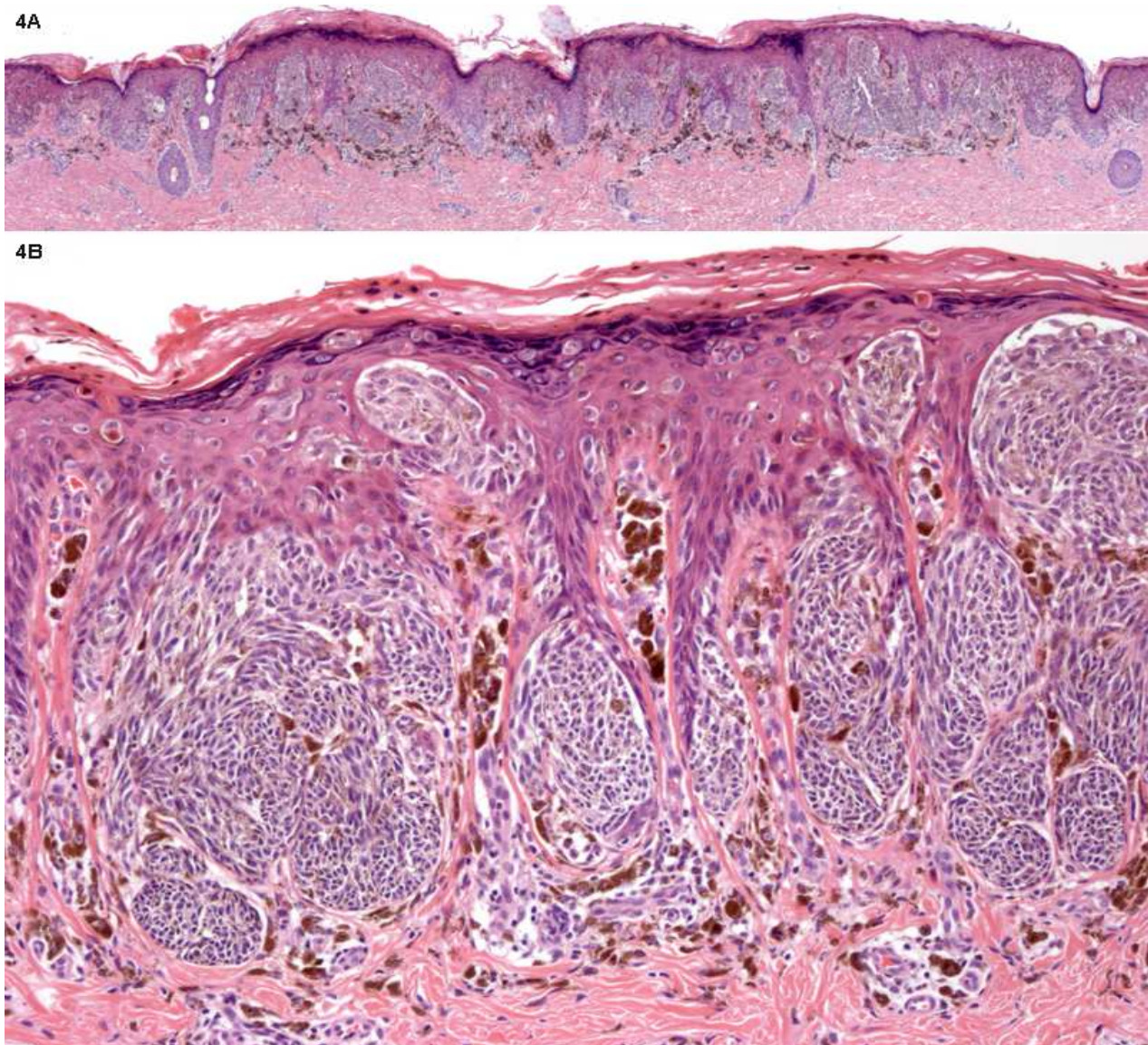


Figure 4. Pigmented spindle cell nevus from right thigh of 11 year old female, 7mm in diameter. 4A) Junctional tumor composed of numerous junctional nests of pigmented melanocytes. Melanophages are present at the base of the lesion. 4B) The melanocytes are oval or spindle-shaped, and contain melanin pigment. Pagetoid suprabasilar spread of single melanocytes and nests of melanocytes is present in this image from the center of the tumor.

Pathology

AST is a heterogeneous group of tumors, from which several categories are emerging with the advent of molecular genetic studies.

The common features of AST are spitzoid features, in which cytologic or architectural atypia exceeds that seen in Spitz nevi, but is insufficient for a definitive diagnosis of melanoma.

The atypical features that may lead to a spitzoid tumor being labeled "AST" include: architectural asymmetry; lack of circumscription; lack of maturation with depth; substantial nuclear pleomorphism; increased cellularity; confluent or sheet-like growth; deep mitotic figures; atypical mitotic figures; and extension into subcutis (Barnhill et al., 1999; Walsh et al., 1998).

Although these criteria are also seen in melanoma, they are present to a lesser degree and extent in ASTs.

It is because of the difficulty in determining the line of demarcation between AST and melanoma on the basis of histologic criteria that AST is a poorly reproducible diagnosis.

Some authors have suggested categorization of AST into tumors at low and high risk for metastasis on the basis of a combination of histologic criteria (Spatz et al., 1999; Walsh et al., 1998), but these classifications are not in widespread use.

Recent advances in molecular pathology have identified several subcategories of ASTs raising the prospect of a refined classification and risk assessment using molecular markers.

Emerging categories of Atypical Spitz Tumor:

1. Desmoplastic Spitz Tumor with HRAS mutations

HRAS-mutant ASTs show distinctive histopathologic and cytogenetic features. They are larger lesions with a predominantly intradermal distribution of melanocytes in horizontal rather than vertical orientation, have marked desmoplasia, characteristic cytologic features with epithelioid melanocytes scattering between thickened collagen bundles, giving them an infiltrating growth pattern. Proliferation rates in the majority of these cases are low. The majority shows a distinctive cytogenetic abnormality comprised of a high-level copy number increase of the entire short arm of chromosome 11 (Bastian et al., 2000; van Engen-van Grunsven et al., 2010).

2. Nodular Spitz Tumor with BRAF and BAP1 mutations

Recently, it was shown that a significant subset of atypical Spitz tumors is characterized by the concomitant presence of BRAF^{V600E} mutation and loss of BAP1 expression, the latter being the result of inactivating BAP1 mutation and/or deletions (Wiesner et al., 2012).

These BRAF^{V600E}/BAP1-negative tumors show distinctive features.

They are non-pigmented, dermal tumors composed of epithelioid melanocytes with abundant amphophilic cytoplasm, well-defined cytoplasmic borders, and vesicular, pleomorphic nuclei with prominent nucleoli. The cells are arranged in large cohesive nests or nodular aggregates.

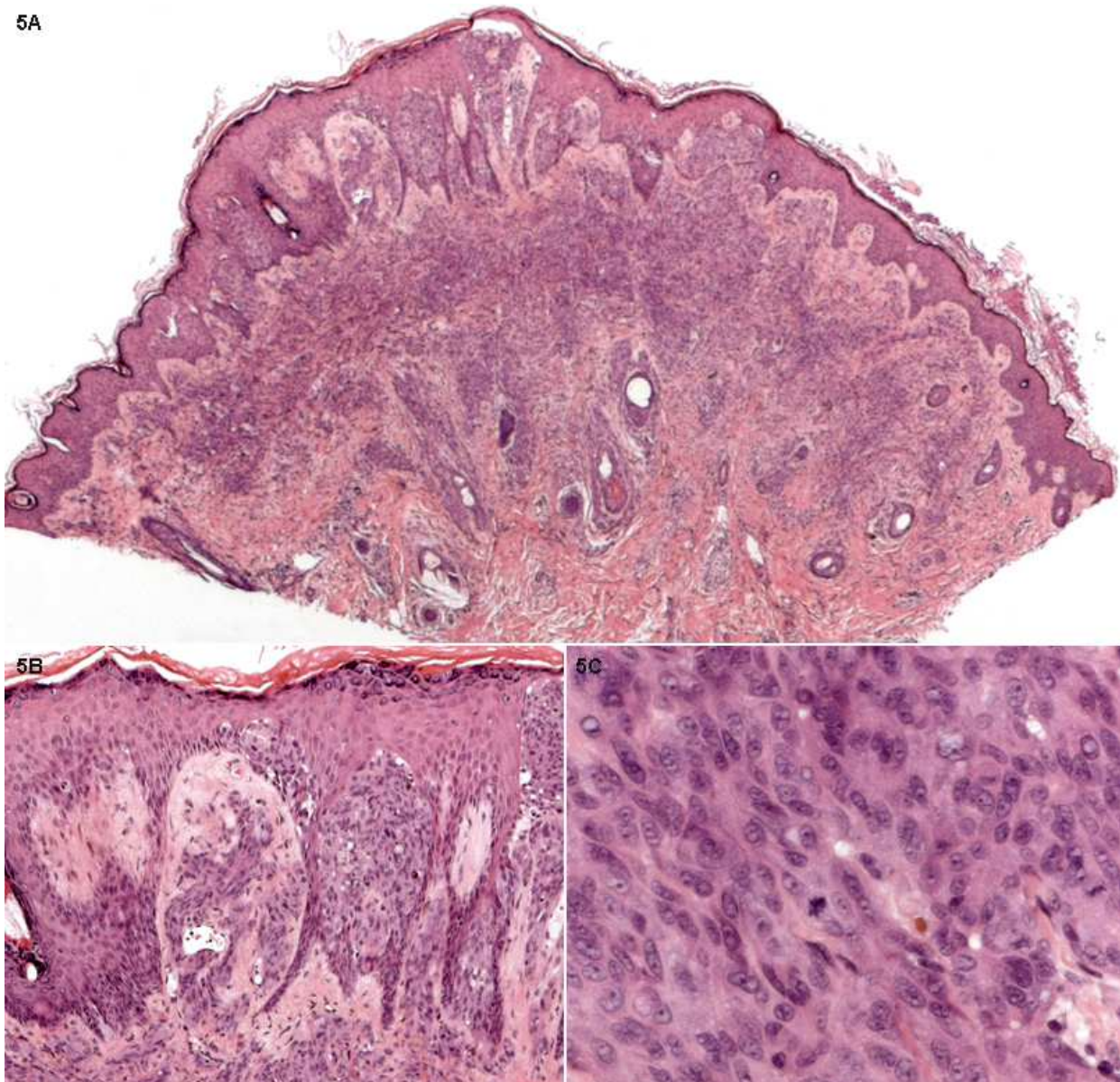


Figure 5. Atypical Spitz tumor from face of 7 year old female, 2.1mm in thickness, with positive sentinel lymph node biopsy, but no recurrence 11 years after diagnosis. 5A) Compound, cellular lesion composed of 5B) epithelioid and oval cells with abundant cytoplasm and mild epidermal thickening and hypergranulosis. 5C) Lesional cells show moderate cytologic atypia, including scattered mitotic figures.

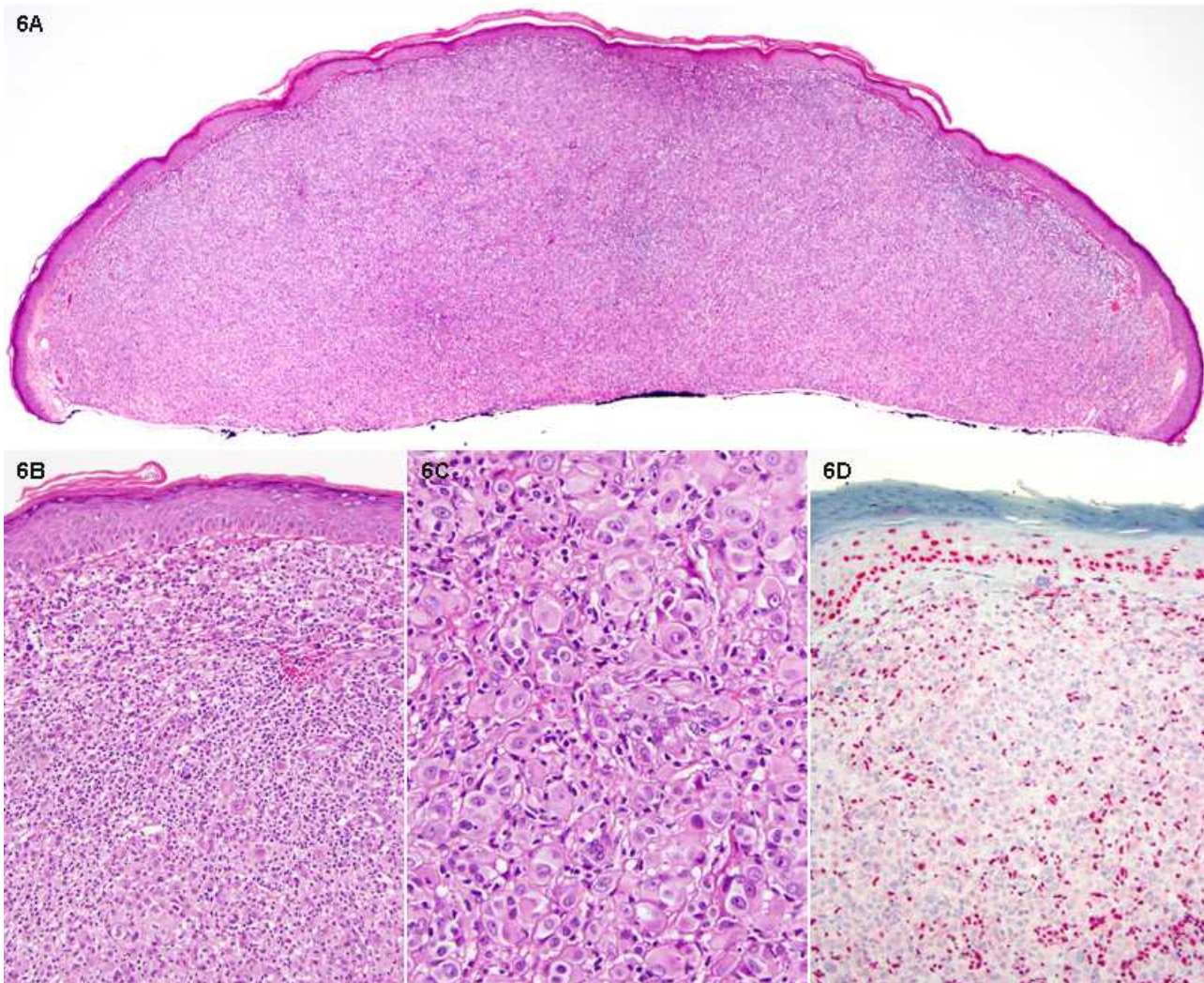


Figure 6. Atypical Spitz tumor with BRAF and BAP1 mutations. 6A) Dome-shaped, fairly symmetrical, cellular compound lesion. 6B) Effacement of rete ridges. Lesion is composed of large epithelioid melanocytes admixed with numerous lymphocytes. 6C) Epithelioid cells have abundant amphophilic cytoplasm, well-defined cell borders, and large vesicular nuclei with conspicuous nucleoli. 6D) Immunohistochemistry shows loss of expression of BAP1 in the nuclei of the tumor cells. Note retention of positive staining in the nuclei of epidermal keratinocytes and dermal lymphocytes.

The overlying epidermis is thinned (rather than thickened as in Spitz nevi), and the rete ridges are effaced. They are often associated with moderate to large numbers of tumor-infiltrating lymphocytes (Wiesner et al., 2012). Loss of nuclear BAP1 expression by immunohistochemistry is a reliable feature to recognize these lesions.

These ASTs have also been observed in a newly described syndrome caused by monoallelic BAP1 germline mutations. Individuals with this condition can have increased numbers of the ASTs described above, and have an increased risk of cutaneous and uveal melanoma (Wiesner et al., 2012). Hereditary BAP1 mutations have also been described in mesothelioma (Testa et al., 2011). The appearance of multiple ASTs with the features described above thus raises the suspicion of germline mutations in the BAP1 tumor suppressor gene and should prompt a careful family

history and physical examination and genetic counseling should be considered.

Treatment

Complete excision. Sentinel lymph node biopsy, as recommended by some physicians, can lead to overtreatment in patients with ASTs.

The SLN positivity rate in these tumors is higher (up to 45%) than that seen in melanoma (15-20%) (Busam et al., 2009; Ludgate et al., 2009; Murali et al., 2008), but sentinel lymph node positivity does not indicate an increased risk of systemic metastatization as poor outcomes are rare in the patients, even with positive sentinel lymph nodes.

Evolution

No recurrence if completely excised. May recur if incompletely excised.

From currently available evidence, they may involve regional lymph nodes (identified if SLN biopsy is

performed), but progression to distant metastasis or death is rare (if "atypical spitzoid tumor" is carefully defined).

Prognosis

Adverse outcomes are rare in the literature to date.

Disease

Spitzoid melanoma

Epidemiology

Spitzoid melanoma may occur in children, but are more common in adults.

Clinics

Commonly occur on the head and the extremities. Typically nodular lesions, often >10mm in size, exhibiting change in shape/size/color. Usually amelanotic, but may be pigmented or variegated in color. Clinically, they may resemble hemangiomas, pyogenic granulomas, or basal cell carcinomas (Bott et al., 2011; Huynh et al., 2005).

Pathology

Spitzoid melanomas often have a junctional component that consists of irregularly-shaped and unevenly distributed nests, often with single melanocytes at the periphery [in contrast to Spitz nevi which are usually well circumscribed with terminal nests at their periphery]. Single melanocytes are not infrequent and suprabasilar pagetoid spread (not confined to the central portion of the lesion) is common. Melanocytes within the nests often lack the cohesion seen in Spitz nevi. The invasive component of spitzoid melanoma consists of an asymmetric proliferation of large, atypical epithelioid and/or spindle-shaped melanocytes, which usually lack pigment. Melanocytic nests, when present, are irregular and confluent. Maturation, i.e. a diminishment in size and/or aggregates of with descent into the dermis, is absent, poor or incomplete. Mitotic figures, including atypical forms in some cases, are present, and are often frequent (>2/mm²) and identified in the deepest part of the tumor. The epidermis may be uneven in thickness, with areas of atrophy and effacement of the rete ridges (in contrast to the hyperplasia seen in Spitz nevi). If the melanoma arose in a pre-existing Spitz nevus, remnants of the nevus may be identified at the periphery of the melanoma. Lymphovascular invasion, perineural invasion and satellitosis may be present (Barnhill, 2006; Crotty et al., 2002; Kamino, 2009; Mooi and Krausz, 2006; Walsh et al., 1998).

Immunohistochemically, HMB-45 tends to show heterogeneous staining in the invasive component of spitzoid melanomas, including in the deep portion of the tumor; in contrast, HMB-45 is usually negative in the deeper dermal component of Spitz nevi (Bergman et al., 1995). The Ki-67 index in spitzoid melanomas is higher (often >10% in the dermal component) than that in Spitz nevi

(Bergman et al., 2001). However, there is considerable overlap in these patterns in Spitz nevi and spitzoid melanomas, and individual features/characteristics cannot be used in isolation to distinguish these tumors. Use of cytogenetic techniques such as fluorescence in situ hybridization (Gerami et al., 2009) or comparative genomic hybridization (Bastian et al., 1999) might be more useful adjuncts for this distinction.

Treatment

As for melanoma. Complete local excision and, in many centers following staging work-up, sentinel lymph node biopsy.

Evolution

As with all melanomas, spitzoid melanomas are malignant tumors, with the potential for distant metastasis and to cause death. Their likely clinical behavior can be predicted based on a variety of clinical and pathologic prognostic factors.

Prognosis

Outcome depends on clinical and pathologic factors that are known to be prognostic in melanoma [e.g. stage, age, Breslow thickness, ulceration, mitotic rate, microsatellites, etc.] (Balch et al., 2009).

Cytogenetics

Note

Spitz nevi typically do not show chromosomal copy number alterations. Increased DNA copy number of 11p (which includes the HRAS gene locus) is seen in ~12% of ASTs and correspond to a type described above (Bastian et al., 2000), but is rarely identified in melanomas. Two-thirds of cases with 11p copy number increase also show oncogenic mutations in HRAS (Bastian et al., 2000). Rare cases show gains in 7q, but could represent a separate category (Bastian et al., 1999).

ASTs of the second category outlined above show an increased frequency of deletions of the BAP1 locus at chromosome 3p21, sometimes involving larger portions of or the entirety of chromosome 3.

Since ASTs are a heterogeneous group of neoplasms, they may show a range of other copy number alterations. However, to date no consistent pattern or other subgroups have emerged beyond the copy number change described above. The presence of multiple aberrations (more than 2) is worrisome and may indicate that the lesion represents melanoma. While, no rigorous analysis of copy number changes in spitzoid melanomas has been performed to date, our experience is that the genomic regions most frequently involved are those described for other melanoma subtypes (Curtin et al., 2005).

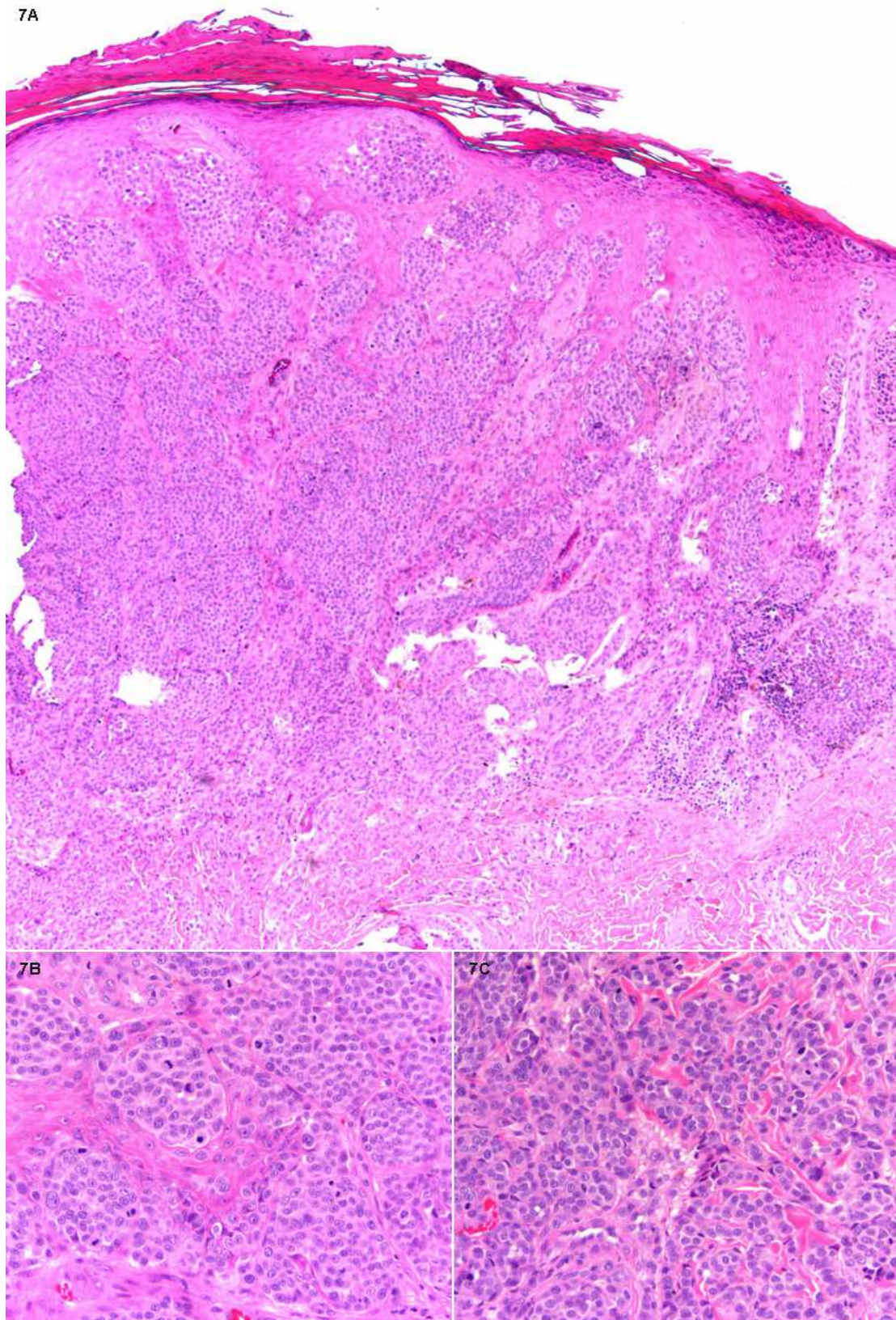


Figure 7. Spitzoid melanoma from the right forearm of a 19 year old patient. The tumor was 1.6mm in thickness and exhibited a mitotic rate of 14 per mm². Sentinel lymph node biopsy was positive, and the patient developed brain metastasis a few years later. 7A) Low power view shows a compound spitzoid melanocytic lesion associated with prominent epidermal hyperplasia. 7B) The superficial dermal component consists of sheets of monotonous epithelioid cells with hyperchromatic nuclei, increased nuclear:cytoplasmic ratios, and numerous mitotic figures. 7C) The deep dermal component consists of atypical cells and the melanocytes lack maturation with depth. Occasional mitotic figures are present.

Genes involved and proteins

Note

Several genetic alterations in melanomas and other types of melanocytic nevi have been discovered in recent years. However, Spitz tumors have been less well characterized, and until recently, the only genomic aberrations described were mutations in HRAS (Bastian et al., 2000). HRAS-mutant Spitz tumors show distinctive histologic features, as described earlier.

A recent study has discovered that a significant subset of atypical Spitz tumors is characterized by the co-occurrence of BRAF^{V600E} mutation and loss of BAP1 expression, the latter often associated with BAP1 mutation (Wiesner et al., 2012). These tumors also show distinct morphological features, as described above.

Therefore, there appear to be distinct genetic subsets of Spitz tumors (with morphologic correlates), the biological and prognostic significance of which is yet to be discovered.

HRAS

Location

11p15.5

Note

HRAS belongs to the Ras oncogene family, whose members are related to the transforming genes of mammalian sarcoma retroviruses. The products encoded by these genes function in signal transduction pathways. Mutations in HRAS cause Costello syndrome, a disease characterized by increased growth at the prenatal stage, growth deficiency at the postnatal stage, predisposition to tumor formation, mental retardation, skin and musculoskeletal abnormalities, distinctive facial appearance and cardiovascular abnormalities. Defects in HRAS are implicated in a variety of cancers, including bladder cancer, follicular thyroid cancer, and oral squamous cell carcinoma. Multiple transcript variants, which encode different isoforms, have been identified for this gene. HRAS mutations have been described in ~15% of Spitz nevi (Bastian et al., 2000), but have not been identified in Spitzoid melanomas (van Engen-van Grunsven et al., 2010).

Protein

Ras proteins bind GDP/GTP and possess intrinsic GTPase activity.

BAP1

Location

3p21.1

Note

BAP1 is a tumor suppressor gene that was thought to function in the BRCA1 growth control pathway.

The protein encoded by this gene localizes to the nucleus and it interacts with the RING finger domain of the BRCA1 protein. More recently, BAP1 has been

shown to play a role in chromatin modification by forming part of multi-protein complexes (such as the polycomb repressive deubiquitinase complex, PR-DUB) that regulate transcription by modification of histones. Germline mutations in BAP1 predispose to the development of several different tumor types, including epithelioid melanocytic tumors (Wiesner et al., 2011), cutaneous melanoma (Wiesner et al., 2011), uveal melanoma (Njauw et al., 2012; Wiesner et al., 2011), mesothelioma (Testa et al., 2011), lung adenocarcinoma (Abdel-Rahman et al., 2011), and meningioma (Abdel-Rahman et al., 2011). A subset of ASTs (~25%) is characterized by BRAF^{V600E} mutation and BAP1 loss (Wiesner et al., 2012).

Protein

Deubiquitinating enzyme that plays a key role in chromatin by mediating deubiquitination of histone H2A and HCFC1. Catalytic component of the PR-DUB complex, a complex that specifically mediates deubiquitination of histone H2A monoubiquitinated at Lys-119 [H2AK119ub1].

Acts as a regulator of cell growth by mediating deubiquitination of HCFC1 N-terminal and C-terminal chains. Interferes with the BRCA1 and BARD1 heterodimer activity by inhibiting their ability to mediate ubiquitination and autoubiquitination.

BRAF

Location

7q34

Note

BRAF encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. Mutations in BRAF are associated with cardiofaciocutaneous syndrome, a disease characterized by heart defects, mental retardation and a distinctive facial appearance. Mutations in BRAF have also been associated with various cancers, including melanoma, thyroid carcinoma, colorectal cancer, non-Hodgkin lymphoma, and adenocarcinoma of lung. A subset of ASTs (~25%) is characterized by BRAF^{V600E} mutation and BAP1 loss (Wiesner et al., 2012).

Protein

Involved in the transduction of mitogenic signals from the cell membrane to the nucleus.

Plays a role in regulating the MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.

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This article should be referenced as such:

Murali R, Scolyer RA, Bastian BC. Skin: Spitz tumors. *Atlas Genet Cytogenet Oncol Haematol*. 2013; 17(1):48-59.
