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Spitz nevi and other Spitzoid lesions: Part I. Background and Diagnoses

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Abstract

Spitz nevi are melanocytic proliferations characterized by spindled and/or epithelioid nevocytic melanocytes. First interpreted as juvenile melanoma, these lesions were later characterized as benign and were observed to affect all age groups. Today, contrasting opinions persist regarding the fundamental benignancy versus malignancy within the spectrum of Spitz tumors. Beyond clinical outcome, this controversy has also been fueled by complex and sometimes convoluted classification schemes based on pathological characteristics. More recently, immunophenotypic and molecular analyses have begun to clarify the etiological nature of these tumors. Recent evidence suggests that histopathological features which suggests more aggressiveness in Spitz tumors relate to mitoses and inflammation.

BRIEF HISTORY

Key points

- The landmark publication on Spitz nevi occurred when Sophie Spitz described pediatric lesions which exhibited features of melanoma
- Recent opinion has been trending toward emphasizing the benign nature of Spitz nevi
- Refinement of clinical and histological subtypes within the Spitz family of lesions has led to a highly complex classification of Spitz tumors

Although cases of perplexing melanocytic lesions have been reported in children as early as a century ago,^{1,2} the landmark publication for Spitz lesions and the origin of the eponym

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came in 1948 from Sophie Spitz. She first described pediatric melanocytic lesions which histologically resembled melanomas and yet lacked their aggressive behavior.³ Spitz termed these lesions ‘juvenile melanomas.’ The title of her article, “Melanomas of Childhood,” encapsulates her interpretation of these lesions as a category distinct from both benign nevi of childhood and adult melanoma.¹ Spitz duly noted that, despite the favorable prognosis, most lesions were histologically indistinguishable from adult melanoma and in fact, there was one fatality among the 13 reported cases.³

Later addendums to her work, however, placed more emphasis on the benign nature of these ‘juvenile melanomas’ and also noted their occurrence in adults.⁴ In 1960, Kernen and Ackerman proposed that Spitz cases with metastases were simply diagnostic errors, and actually melanoma.⁵ Concepts of the ‘atypical Spitz tumor’ began with the introduction of the term by Huarte in 1970,⁶ and the use by Smith et al. of the term ‘spindle and epithelioid cell nevus with atypia and metastasis’ in 1989.⁷ No disease progression was observed in either report. Nevertheless, Barnhill et al. in 1999 reported one death out of 30 patients who supposedly had ‘typical’ Spitz nevi.¹ Of note, both fatal cases described by Spitz and Barnhill occurred in females who had reached puberty. The role of hormones in modifying the risk of mortality from melanoma was emphasized by Spitz herself and remains an open question. Because of the small but uncertain risk, much effort has been placed in defining the prognostically unfavorable Spitz tumors.

Currently, the clinical and histological space of Spitz-type lesions has become tremendously complex. For simplicity’s sake, the general term, “Spitz tumor”, will be used in this article to encompass the range of lesions in this category. On the one end of the spectrum, the common Spitz nevus (CSN), with its relatively banal histology, is still recognized as a benign proliferation that frequently occurs in children. On the other end of the spectrum, certain Spitz tumors exhibit such extensive pleomorphic features that the differential of melanoma is difficult or impossible to rule out; thus, the term, ‘Spitzoid melanoma,’ has been used.⁸ Occasionally, Spitzoid melanomas are retrospectively diagnosed when an adverse outcome is associated with a Spitz tumor. Barnhill and Gupta have reported that the term “Spitzoid melanoma” has been applied to melanomas initially misdiagnosed as Spitz nevi, controversial Spitz tumors (with or without lymph node involvement, and/or genetic aberrations, regardless of progression), as well as conventional melanomas.⁸ Thus, there is also disagreement among diagnosticians even within the Spitzoid melanoma category. Finally, the challenge lies within a subset of lesions that fall in between the two extremes. The literature has referred to these lesions as “Spitz nevus with atypia”, “atypical Spitz nevus”, atypical Spitz tumor”, “malignant Spitz nevus”, “Spitzoid tumor of uncertain malignant potential”, and “diagnostically controversial Spitzoid melanocytic tumors”.^{7, 9–11} Terms such as “minimal deviation melanoma”, and “borderline nevomelanocytic neoplasm” also have been used to set these lesions apart from conventional melanoma.^{12–15} Some authors argue that this heterogeneous “atypical Spitz tumor” (AST) category is warranted to encompass Spitz tumors with varying features of atypia and unknown malignant potential,^{1, 8} while others counter that this category is only a linguistic wordplay for inaccurately diagnosed malignant melanoma.^{7, 11, 16, 17} A recent effort to classify melanocytic tumors of uncertain malignant potential (MELTUMPs) according to reproducible histopathological criteria suggests that an intermediate group biologically distinct from either benign nevi or conventional melanomas (eg. ASTs) is actually warranted.¹⁸ This landmark study found that even experts were unable to reliably predict the outcome of a group of atypical Spitz lesions. In addition, it demonstrated that only three criteria hold significant predictive value for outcomes in evaluations of MELTUMPs: mitotic activity, mitoses near the base, and inflammation.¹⁸ Currently, inadequate histologic criteria exist to accurately diagnose these intermediate Spitzoid forms^{16, 19, 20} and thus

further studies leveraging molecular insights and richer clinical datasets are absolutely essential to better define these lesions.¹

CLINICAL FEATURES

Key points

- Younger age is associated with more likely benign behaving Spitz nevus

Table 1 offers a comparison of various clinical features suggestive of typical Spitz nevi versus ASTs. Greater attributes from the latter group calls for closer scrutiny to rule out melanoma.

Age—The weight of historical evidence is that age is a primary discriminant between Spitz tumors and more common forms of cutaneous melanoma. Unfortunately, this creates its own diagnostic bias since dermatopathologists may be reluctant to diagnose bona fide melanomas in a young individual.²¹ Since many Spitz tumors occur between 10 and 20 years of age¹, their distinction from melanoma is duly influenced by consideration of patient age. The overall effect is one of circular logic- since Spitz tumors occur more frequently in younger patients, dermatopathologists are more likely to diagnose Spitz lesions in this age group thereby further driving the estimates upward. An algorithmic approach has been introduced in attempt to quantify the predictive probability of age intervals on the differential between melanoma and Spitz nevi. This equation utilizes Bayes rule along with previously published data to provide the conditional probability of Spitz nevus given the patient's age.²² Among other findings, the results demonstrated that in patients younger than 4 years, lesions are more likely to be Spitz nevi regardless of the calculated *a priori* probability. On the other hand, lesions in patients older than 8 years depend more on the calculated probability.

Morphologic characteristics—Other clinical characteristics may also aid in recognizing problematic variants of Spitz tumors. CSN are frequently less than 10 mm in diameter, most being smaller than 5–6 mm across. A size exceeding 10 mm is regarded as abnormal.¹ They most often feature symmetry, smooth topography, and sharply demarcated borders.^{8, 20} CSN are typically pink to red, due to limited melanin content and increased vascularity (Fig 1A–D).²³ However, approximately 10% of CSN are pigmented (Fig 1E–G),⁸ with colors ranging from tan, brown, to even black.²⁴ Deviation from these features may indicate a more worrisome lesion.²⁵

In terms of distribution, the most frequent sites for CSN include the head and neck regions (37%) and lower extremities (28%).²³ Fewer lesions, perhaps only 6%, present on the back and may be a sign of a more atypical lesion. Lesions are typically solitary, with rare accounts of multiple Spitz nevi. When multiple, an agminated (grouped) or disseminated pattern may be seen (Fig 1H).²⁶ The etiology of multiple lesions is unclear,²⁷ but various theories have been proposed including history of sunburn, trauma or inoculation, as well as genetic predisposition.^{28–30}

Dermatoscopic features—The most typical, pink CSN exhibits little pigmentation on dermoscopy and features a characteristic dotted vascular pattern (Fig 2). Pigmented Spitz nevi, or Reed's nevi, appear very different dermatoscopically; typically exhibiting either a 'starburst' or 'globular' pattern. The first is characterized by diffuse blue to black pigmentation that extends into radial streaks at the periphery, contributing to a stellate appearance. The second pattern consists of prominent brown to grey-blue pigmentation bordered by a peripheral rim of discrete pigment globules.^{31, 32} Lesions may present an evolving dermatoscopic pattern from globular to starburst, and some may further change by losing the starburst pattern in favor of a homogeneous blue-brown pigmentation with or

without central reticular pigmentation.^{33, 34} Attempts to integrate clinical, dermatoscopic and histopathological features in order to evaluate Spitz tumors have not been straightforward. Although the standard of practice is to completely remove atypical melanocytic lesions for diagnosis, dermoscopy can define potential areas for partial sampling if incisional biopsies need to be performed.³⁵ Additionally, asymmetry appreciable by dermoscopy is a frequent indicator of histopathological atypia in Spitz tumors.²⁴

Clinical differential diagnoses

ASTs generally fail to present in a specific clinical pattern. Besides resembling melanoma, ASTs can also clinically simulate non-melanocytic lesions such as dermatofibroma.³² Classic differentials for CSN and ASTs include congenital, acquired, and dysplastic variants of the melanocytic nevus, as well as a sundry of non-pigmented lesions such as pyogenic granuloma, hemangioma, angiofibroma, keloid, and xanthogranuloma.²³

HISTOPATHOLOGY

Key points

- Classic Spitz nevi feature neat organizational attributes such as symmetry, maturation, distinct margins, small size, and more often demonstrate epidermal hyperplasia, Kamino bodies, and junctional clefting
- Ulceration, significant Breslow thickness, increased number of mitotic figures, and deep and atypical mitotic figures may be associated with metastatic behavior
- Still, most histopathological criteria remain poorly predictive in cases that overlap between ASTs and melanoma

The available literature describes a range of contrasting histopathological criteria for diagnosing Spitz tumors.¹ Table 2 outlines the prototypic histopathological findings in Spitz nevi as well as more concerning architectural and cytological attributes.^{1, 36} Figure 3 provides histopathological images of these features. It is important to keep in mind, however, that while an accumulation of atypical attributes may suggest higher risk, most histopathological features have poor predictive value in differentiating benign from malignant behavior in ASTs.^{18, 37}

General histopathological characteristics

CSN are predominantly compound in architecture, with a minority of solely intradermal or intraepidermal forms.³⁸ It is possible that the majority of Spitz nevi are excised while in the compound stage when nevic elements are more recognizable. Like other melanocytic nevi, CSN are thought to evolve through all three distinct junctional, compound, and intradermal phases.³⁹

The epidermis remains notably undisturbed in most CSN. Melanocytic nests neatly weave between keratinocytes, unlike the disordered and obliterative patterns seen in melanoma. Eosinophilic globules, commonly known as Kamino bodies, may be present intraepidermally, as well as in aggregates at the dermoepidermal junction.⁴⁰ Although also featured in melanoma, distinct aggregates of Kamino bodies are reassuring as more suggestive of classic Spitz nevi.⁴⁰ Kamino bodies are thought to represent apoptotic keratinocytes and melanocytes, but have not held up to this theory in apoptosis labeling studies, so their true mechanism remains unclear.⁴¹ Other characteristic epidermal features include a regular pattern of symmetrical epidermal hyperplasia, as well as clefting due to retraction artifact around junctional nests.^{8, 19} Overall, growth patterns in Spitz nevi are perceived more as ordered versus disordered.^{38, 39} Replacement of orderly attributes with more haphazard ones should raise concern for increasingly ASTs and possibly, melanoma.

Concerning histopathological attributes

Several histological features are more worrisome for more aggressive behavior although there is not a single attribute which is definitively diagnostic.¹ In one study, increasing asymmetry, poor circumscription, thicker and deeper extension, and ulceration all predict more metastatic potential.³⁶

In intraepidermal forms of Spitz nevi, the main melanocytic growth pattern is that of junctional proliferative nests.³⁸ Although Pagetoid spread of individual melanocytes is not uncommon⁸, extensive zones of Pagetoid distribution, involvement of the upper epidermis, spread in a single cell or small nested pattern, extension of Pagetoid growth and expansion of the junctional component beyond the dermal component may be considered as worrisome features. There is a distinct but rare variant of Spitz tumor termed the “Pagetoid Spitz nevus” that may be difficult to distinguish from *in situ* or microinvasive melanoma.³⁸

Banal Spitz nevi should feature zonation with depth, i.e. uniformity of size, shape and spacing of melanocytic nests and fascicles within the same horizontal plane; deeper cells should exhibit greater maturation as reflected in decreasing cellular density, progressively smaller nests with transition into single cells, and the nondisruptive infiltration of these individual melanocytes among collagen bundles.^{25, 37} Hence, marked lateral heterogeneity and persistence of deep nests of considerable size and a pushing deep border all represent more atypical Spitzoid features. Cellularity and confluence also correlate with maturation.¹ More aggressive ASTs may exhibit expansile and densely confluent cellular aggregates at deeper levels of the dermis, even replacing the dermis, with limited or no maturation. However, these two parameters are subjective and therefore, difficult to quantify. In addition, the significance of such findings in children is not clear.³⁷

The dermal mitotic rate is also quite useful in the evaluation of Spitz tumors. More deeply seated mitotic activity, involving the inferior dermis and/or subcutaneous layer of a lesion's base, seems to carry a poorer prognosis than superficial mitoses.⁸ The presence of deep dermal mitoses in ASTs is associated with unfavorable outcomes such as metastases and tumor-related death.¹⁸

While an overall mitotic rate $> 5/\text{mm}^2$ in an AST has been correlated with risk of metastasis,³⁶ dermal mitotic activity (as low as $3/\text{mm}^2$) serves as an independently significant feature in distinguishing melanoma⁴² and Spitzoid melanoma⁴³ from Spitz nevi. However, there have not been sufficient analyses to define a precise mitotic rate which would allow for discrimination between benign and malignant behavior, however, an overall mitotic rate of $> 2/\text{mm}^2$ is considered alarming in dermatopathologic evaluation of these tumors.

Cytological atypia is a standard feature of many malignancies though inter-observer agreement may be low.²⁵ ASTs can exhibit more cellular heterogeneity and disorganization. Cytology favoring malignancy include higher nuclear-to-cytoplasmic ratios, ill-defined cytoplasmic borders with more granular-appearing cytoplasm,³⁸ hyperchromatism, abnormal nuclear contours with a thickened nuclear membrane, as well as enlarged and pink nucleoli.⁸

Histopathological variants and differential diagnoses

Many now recognize the pigmented spindle cell nevus (Reed's nevus) as a pigmented subtype of a CSN.^{44, 45} Features include an organized silhouette, relative uniformity, and overlapping attributes with melanoma such as epidermal hyperplasia, Pagetoid spread, and dermal nesting.^{38, 45}

The desmoplastic Spitz nevus is a variant that may have histological features which overlap with dermatofibroma, desmoplastic cellular blue nevus, or desmoplastic melanoma.⁴⁶ This subtype can be the principal presenting morphology in the recurrence that develop after the incomplete removal of a CSN.^{47, 48} Immunohistochemical staining may assist differentiation from other diagnoses including desmoplastic melanoma.^{46, 49}

The combined nevus, which can contain Spitz components, should also be considered in the diagnosis of a Spitz tumor.¹ This lesion is defined as the combination of more than one nevus type, leading to the asymmetry and phenotypic heterogeneity that can be mistaken for melanoma.⁵⁰

For the school of thought in which Clark's nevus is synonymous for dysplastic nevus, some experts have introduced the "Spark's nevus" variant. This entity displays a Clark's/dysplastic nevus architecture (consisting of a lentiginous pattern, bridging nests, fibrosis, and lateral extension of the junctional component), while featuring a Spitzoid cytology of epithelioid and/or spindled cells.⁵¹ However, for those who eschew eponyms, the "Spark's" nevus may not be an ideal designation.

ADDITIONAL TESTS

Key points

- in CSN compared to melanoma, Ki67 is stained in fewer cells, HMB-45 exhibits differential staining at certain lesion depths, while S100A6 is stained strongly and diffusely
- Cytogenetic techniques reveal amplifications in chromosome 11p in a minority of Spitz nevi
- Most Spitz nevi exhibit a distinct mutation profile from common nevi and melanoma, featuring more *HRAS*, rather than *BRAF* or *NRAS* mutations

Immunohistochemistry

Immunohistochemical markers have been used in an effort to better discriminate Spitz tumors from melanoma. MIB-1 stains Ki-67, a proliferative marker expressed in a greater percentage of cases and larger proportion of nuclei in melanoma compared to CSN. An atypical proliferation index (Ki-67 expression) of between 2–10% in one study, or greater than or equal to 10% in another study have been suggested as surrogates to atypia.^{52, 53} There is a drop in Ki-67 staining as one progresses from melanoma to ASTs to CSN and finally to banal conventional nevi; Ki-67 has thus been proposed as a method of risk stratification for Spitz tumors.^{1, 54, 55}

Other markers include HMB-45, which is expressed more prominently in the superficial aspects of CSN but persist in deeper dermal levels in melanoma.^{47, 56} There is a diminished proliferation with increasing depth of dermal component paralleling decreasing mitotic rate and cyclin D1 expression in benign Spitz tumors.¹ Also compared to melanoma, CSN exhibit lower indices of staining for fatty acid synthase, p53, Bcl-2 and Cdc-7.^{53, 54, 57} S100 and Mart-1 stains more weakly and diffusely in Spitz nevi compared to melanoma.^{1, 58} In contrast, the S100A6 subtype exhibits more intense and diffuse expression in Spitz nevi, and is weak and patchy in melanoma.⁵⁹ Recent immunophenotypic studies also show more prominent dermal p16 reactivity in CSN versus melanoma, while ASTs showed intermediate levels.⁶⁰ Similarly, p16 is stained more intensely in desmoplastic Spitz tumors, setting them apart from desmoplastic melanoma, where it is largely absent.⁴⁹ One study showed CD99 to be preferentially expressed in Spitzoid malignant melanoma (56% cases showed diffuse expression) over Spitz nevus (5% cases showed focal staining and no diffuse staining).⁶¹

Other immunostains, such as elastin, have been used to distinguish melanoma from associated nevi by staining elastic fibers still intact between nevic nests.⁶² This may be useful when applied in the same technique for melanomas associated with Spitz nevi. A recent review suggests that greater concordance of diagnoses was observed when an immunohistochemical panel was added to the evaluation of hematoxylin and eosin stain along with patient age.⁶³ It is important to note, however, that no single or panel of immunohistochemical markers is able to currently refine diagnoses within the Spitz spectrum of lesions.

Molecular analyses

Analysis of the entire genome using comparative genomic hybridization (CGH) has revealed that a subset of Spitz tumors harbor amplifications in chromosome 11p, a unique chromosomal aberration not commonly seen in melanoma.⁶⁴ The tumor cells in these lesions featured at least a 3-fold increase in copy number as shown by fluorescent in situ hybridization (FISH).⁶⁵ The 11p area of the genome contains the *HRAS* gene, and copy number gains along with point mutagenesis of this gene have been shown to exist in Spitz tumors. Tumors with 11p amplifications share several histological similarities to melanoma including a larger size, prominent intradermal component, infiltrative growth pattern, and significant desmoplasia.⁶⁵ The majority of Spitz cases are diploid and even when copy number alterations are found, they usually only involve a minority of cells in the lesion.^{58, 65} While the 11p amplification is characteristic of Spitz nevi and has set the premise of utilizing cytogenetics as a diagnostic adjunct,⁶⁶ separate studies have also demonstrated that some Spitz nevi share certain chromosomal anomalies with melanoma; for example, the loss of heterozygosity at chromosome 9p.^{67, 68} Still, several algorithms have incorporated CGH and FISH as adjunctive techniques in order to enhance diagnostic precision of difficult Spitzoid lesions^{69, 70}; however the utility of FISH in deciding on patient management remains to be established. With the exception of Spitz nevi, other melanocytic nevi generally do not appear to harbor significant copy number alterations as compared to melanoma (Fig 4A and B).

Attempts to utilize mutation analysis to distinguish Spitzoid lesions from melanoma have yielded limited and inconsistent results. Unlike other melanocytic proliferations, the full mutational landscape of Spitzoid lesions is still being uncovered. Since *HRAS* amplifications occur in CSN, early studies identified activating *HRAS* mutations in these lesions.⁶⁵ Initial reports found that Spitz nevi do not typically contain *BRAF* and *NRAS* mutations, which are commonly found in other types of melanocytic nevi and melanoma, including Spitzoid melanomas;^{71–76} thus it appeared that the presence of *HRAS* mutations favors CSN (Fig 4D) while *BRAF* mutations predict melanoma. This seemingly simplistic view has been challenged when more recent studies found that CSN in fact harbored mutations in *BRAF* (5–20%) and *NRAS* (0–5%) (Fig 4C).^{67, 77, 78} As it stands, the genetic profiles of melanoma, acquired and congenital nevi and Spitz tumors all point to activation of the RAS pathway (Fig 5) although the basis for the selectivity of distinct pathway components (ie. *HRAS* vs. *BRAF*) is not known.

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ABBREVIATIONS

CSN	common Spitz nevi
AST	Atypical Spitz tumor
CGH	comparative genomic hybridization
FISH	fluorescent in situ hybridization

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Figure 1.

Clinical photographs of Spitz nevi. **A**, Classical Spitz nevi most frequently occur on the face. **B-D**, They appear as pink to red, well-demarcated, dome-shaped papules that can be ulcerated. **E**, A minority of Spitz nevi are pigmented. **F, G**, Dense blue-black pigmentation is characteristic of the Pigmented Spindle Cell Nevus of Reed, which some consider a variant of Spitz. **H**, Multiple Spitz nevi are rare and often occur within a hyperpigmented patch such as a cafe-au-lait macule. (Photographs courtesy of Antonio Torrelo, MD)

Figure 2. Clinico-dermatoscopic correlation of a classical Spitz nevus. **A-B**, Total body photography captured the rapid growth of a Spitz nevus, from previously normal skin. **C**, Dermoscopy shows the typical dotted vessel pattern on a background of little pigmentation for a classical, non-pigmented Spitz nevus. (Photographs courtesy of James Grichnik, MD, PhD)

Figure 3.

Histopathological features of Spitz-type melanocytic lesions. **A**, Classic Spitz nevus. This example is a symmetric polypoid lesion, with predominant dermal nests of epithelioid cells. *Inset*: cells in Spitz nevi are large, polygonal-round, with low nuclear-cytoplasmic (N/C) ratio, an amphophilic cytoplasm, and distinct nucleoli. **B**, Classic Spitz nevus. There is epidermal hyperplasia overlying dermal nests. *Inset*: A Kamino body (eosinophilic globule) is present at the dermo-epidermal junction. **C**, Atypical Spitz tumor. This compound melanocytic tumor is relatively symmetric in its epidermal and superficial dermal aspects, however, has a deep peri-adnexal component. Patches of lymphocytic inflammation are also seen. *Inset*: the dermal cells are spindle shaped and have a fascicular growth pattern, and cytological atypia is seen. **D**, Atypical Spitz tumor. The epidermal/junctional nests are relatively symmetric, there is some thinning of the overlying epidermis, and atypical cells are growing in a fascicular distribution. **E**, Spitzoid melanoma. This large tumor is thick (> 1 mm in depth), is asymmetric, has a pushing border, and maturation of melanocytes are not appreciated. **F**, Spitzoid melanoma. Surface ulceration. **G**, Spitzoid melanoma. Pagetoid spread is a common finding in Spitz-type lesions. In Spitzoid melanomas, the Pagetoid spread expands beyond the epicenter of the lesion and is present at the peripheral aspects of the lesion. **H**, Spitzoid melanoma. Cytological atypia is pronounced. **I**, Spitzoid melanoma. Mitotic figures are frequently seen in Spitzoid melanomas, especially in the deeper aspects of the tumor. **J**, Spitzoid melanoma. The tumor infiltrates the subcutaneous adipose tissue.

Figure 4.

Molecular insights into Spitzoid lesions. **A**, Comparative Genomic Hybridization (CGH) data comparing copy number differences between melanoma and **B**, melanocytic nevi. Copy number increases (green) and decreases (red) of chromosomes are provided. Except for Spitz-type nevi (at chromosome 11p), most other types of nevi are genomically intact compared to melanoma. (Reprinted from Am J Pathol 2003, 163:1765–1770 with permission from the American Society for Investigative Pathology.) **C**, Spitz nevus, AST and other Spitzoid lesions demonstrate less *BRAF* and *NRAS* mutations compared to melanoma. **D**, However, *HRAS* mutations are noted while being very rare or absent in melanoma. (Adapted from Am J Surg Pathol 2005; 29: 1145–51 and *Mod Pathol 2006; 19: 1324–32.)

Figure 5.

The signaling components of the RAS/MAPK pathway found to harbor activating mutations in various types of nevi and melanoma. Most commonly known are the BRAF mutations in acquired nevi, superficial spreading melanomas (SSM), and nodular melanomas (NM); HRAS mutations in Spitz nevi and Spitzoid lesions, NRAS mutations in congenital nevi, KIT alterations in acral and mucosal melanoma, and GNAQ and GNA11 mutations in ocular melanoma and blue nevi. Mutated GNAQ and GNA11 can alternatively activate MAPK.⁷⁹ An approximate prevalence of each mutation is also listed for each type of lesion. Activation of this pathway triggers a cascade of events that eventually upregulates several transcription factors, including MITF, which plays a critical role in melanocyte survival and melanocytic neoplasia.

Table 1

Clinical Features of Classic Spitz Nevi v. Atypical Spitz Tumors

Clinical feature	Classic Spitz nevi	Atypical Spitz tumors
Age	<10 years old	10–20 years old
Location	extremities, face, neck	back
Size	<5–6 mm diameter	>1 cm
Shape	symmetrical, dome-shaped	increasing asymmetry
Border	well-defined	irregular
Surface	smooth	irregular, ulcerated
Color	pink/reddish	irregular
Family hx of melanoma	no	yes

Table 2**Histopathological Attributes of Classic Spitz Nevi v. Atypical Spitz Tumors**

Attribute	Classic Spitz nevus	Atypical Spitz tumors
Organization	orderly, nondisruptive	haphazard, infiltrative
	symmetrical	asymmetrical
	sharply demarcated	poorly circumscribed
	intact, hyperplastic epidermis	disrupted, ulcerated epidermis
	aggregates of Kamino bodies	absent or few Kamino bodies
	junctional clefting	lack of junctional clefting
	lack of deep involvement	subcutaneous involvement
	limited Pagetoid spread, lower epidermis	prominent, single-cell Pagetoid spread, beyond epidermal nests
	diminished cellularity with depth	confluence, dense cellularity
	zonation: side-to-side uniformity	lack of zonation
	smaller nests with depth	persistent, expansile deep nests
Proliferation	mitoses $<2/\text{mm}^2$	mitoses $\geq 2\text{--}6/\text{mm}^2$
Cytology	spindled or epithelioid cell type	more heterogeneous cell types
	ground glass or opaque cytoplasm	granular, dusty cytoplasm
	low nuclear-to-cytoplasmic ratio	high nuclear-to-cytoplasmic ratio
	delicate, dispersed chromatin	hyperchromatism
	uniform nucleoli	large, eosinophilic nucleoli

Adapted from Spatz et al. 1999 and Barnhill et al. 2006