

Spitz Nevus and Atypical Spitzoid Neoplasm

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Spitz nevus (SN) and Spitzoid malignant melanoma (SMM) represent benign and malignant counterparts at both ends of the spectrum of Spitzoid lesions. Atypical Spitzoid neoplasm (ASN) is a poorly defined and characterized category of melanocytic tumors with histologic features of both benign Spitz nevi and malignant melanomas. The group of ASN represents a mixture of Spitz nevi with atypical features and Spitzoid melanomas. However, at the current moment in time, histopathologists are not capable of differentiating between the 2 in some cases and are forced to place them in this ambiguous category, where the behavior of these lesions cannot be predicted with certainty. Because this group encompasses both benign and malignant lesions, and perhaps also a separate category of melanocytic tumors that behave better than conventional melanomas, some of these neoplasms can metastasize and kill patients, whereas others have no metastatic potential, and yet others might only metastasize to regional lymph nodes. Although diagnostic accuracy has improved over the years, many of these lesions remain controversial, and there is still poor interobserver agreement in classifying problematic Spitzoid lesions among experienced dermatopathologists. The objective of this review article is to summarize the most relevant information about SN and ASNs. At this time histologic examination remains the golden standard for diagnosing these melanocytic neoplasms. We therefore concentrate on the histopathologic, clinical, and dermoscopic aspects of these lesions. We also review the most recent advances in immunohistochemical and molecular diagnostics as well as discuss the controversies and dilemma regarding whether to consider sentinel lymph node biopsy for diagnostically ambiguous melanocytic neoplasms.

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It has become apparent over a period of years that even when a histologic diagnosis of malignant melanoma has been made in children the clinical behavior rarely has been that of a malignant tumor—with these insightful words Sophie Spitz begins her article on juvenile melanomas published in 1948.¹ Spitz believed that these lesions were juvenile melanomas incapable of metastasizing. Years later it became apparent that the lesion described by Sophie Spitz was one type of a benign nevus, which was subsequently named after her. However, even in the series of 13 cases included in Sophie Spitz's original article, one lesion was a melanoma that killed a 12-year-old patient. This was the beginning of a long road of diagnostic uncertainty and discordance among expert dermatopathologists in the domain of Spitz-

zoid tumors.² Today, more than half a century after the first description of Spitz nevus (SN) and despite the presence of more refined criteria and molecular diagnostic tools, the distinction between SN with atypical features and Spitzoid malignant melanoma (SMM) remains difficult at times, and prediction of the biological behavior of these lesions is often utterly impossible.

Spitz Nevus

Definition

Spitz nevi are benign melanocytic nevi composed of large epithelioid, oval, or spindled melanocytes arranged in fascicles.

Synonyms

Spindle and epithelioid cell nevus. Pigmented spindle cell nevus is considered by some authorities to be a separate entity, whereas others believe that it is a variant within the spectrum of Spitz nevi.

Epidemiology

SN are commonly seen in children but are relatively uncommon in adults. They account for approximately 1% of excised

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Figure 1 A dome-shaped smooth pink papule on the cheek of a child.

nevi in children.³ About one-half to two-thirds appear in the first 20 years of life.^{4,5} Congenital SN have been reported.⁶ SN may occur in all racial groups but are more common in white patients.

Clinical Presentation

SN usually present as a single, dome-shaped papule or nodule with a diameter of 6 mm or less (Fig. 1). However, larger lesions have been reported. Most lesions occur on the face and head in children or lower extremities in young adults, particularly women.⁷ Their color may vary from nonpigmented through pink to red-brownish and even black. SN commonly appear suddenly and grow rapidly for a period, after which they remain static. However, color changes, bleeding, and pruritus may occur. Unusual Spitz variants include grouped (agminated)⁸⁻¹⁰ or disseminated SN.¹¹ Eruptive SN have also been described.¹²

SMM is in the differential diagnosis of SN. There is no characteristic clinical appearance of SMM; however, some features characteristic of melanoma in general may be helpful, for example, large or expanding size, irregular borders and pigment distribution, surface changes, such as ulceration and loss of skin markings, or presence of pain and pruritus.¹³ Although SN are usually less than 1 cm, melanomas in children may be large and clinically striking.¹⁴ According to some authors' experience SMM are usually amelanotic.⁴

Dermoscopic Features

Dermoscopy as a form of *in vivo* microscopy has been shown to improve the diagnostic accuracy of pigmented lesions and amelanotic neoplasms.¹⁵ The nonpigmented SN may demonstrate one of many dermoscopic patterns, among which the starburst, globular, and atypical (multicomponent) predominate.¹⁶ Additional features are dotted vessels and network depigmentation. Dermoscopy may be useful in the preoperative evaluation of controversial melanocytic neoplasms.¹⁷ In a study of 83 Spitzoid lesions (histologically subspecified into classic SN, pigmented SN, Reed's nevus, and atypical Spitzoid neoplasm [ASN]), 7 lesions determined to be atypical (multicomponent) by dermoscopy were devoid of histopathologic features of atypia.¹⁶ Confocal microscopy (in vivo reflectance confocal microscopy) has been used in an attempt to improve the diagnosis of Spitzoid neoplasms; however, it does not reach a vertical depth required for accurate diagnosis of these lesions and therefore is not able to determine the presence or absence of certain characteristic features.¹⁸

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Histopathologic Features

SN is a proliferation of large melanocytes with epithelioid and/or spindled morphology, arranged in nests or fascicles.¹⁹ SN are usually compound, although junctional and intradermal lesions are not uncommon.^{20,21} Compound SN are symmetric, well circumscribed, and often wedge-shaped, with large nests of melanocytes in the epidermis and in the underlying dermis (Fig. 2A). There is sharp lateral demarcation. The melanocytes are arranged in nests, relatively uniform in size and shape, and, typically, with vertical orientation (Fig. 2B). There are often artifactual clefts between the melanocytic nests and the adjacent epidermis (Fig. 2C). Melanocytes may be seen above the dermal epidermal junction (pagetoid spread of melanocytes), predominantly in the lower half of the epidermis. This process is usually not diffuse and often confined to the center of the lesion; however, it can be quite marked in developing junctional SN in young children.²² Most SN show maturation of the melanocytic nests and melanocytes with their descent into the dermis, defined as progressive reduction of melanocytic nests and cellular size from the top to the bottom.²³

Melanocytes in the dermis are mostly nested or arranged in fascicles and do not form sheets. The base of the lesion may be flat, and there are often single melanocytes infiltrating in between collagen bundles in the reticular dermis. When the subcutaneous fat is involved, only the upper part is usually affected in the form of a nodule. In SN mitotic figures may be seen, but they are usually not numerous, seen in the mid- to upper portion of the lesion, and are more prevalent in the compound type of SN compared with the junctional and intradermal SN.²³ Some authors suggest a cut-off number of up to 2 mitoses per lesion for benign SN.²⁴ However, it should be noted that numerous mitoses can be present in rapidly growing SN as well as in recurrent, regressing, or traumatized ones.²⁵ Atypical mitoses are rare if seen at all. Necrosis *en masse* is absent. The melanocytes of SN are plump, have abundant cytoplasm, and contain a centrally located vesicular nucleus, often with prominent nucleolus. The melanocytes may be of different shape: round, oval, polygonal, sometimes achieving bizarre shapes.⁵ Multinucleated cells may be present as well. The cytoplasm of the epithelioid cells may have ground glass appearance. Melanin is usually absent. If present, in most SN the melanin pigment is symmetrically distributed, and there is absence of melanin at the deepest level of the lesion, whereas in most melanomas, the pigment is unevenly scattered and present also at the

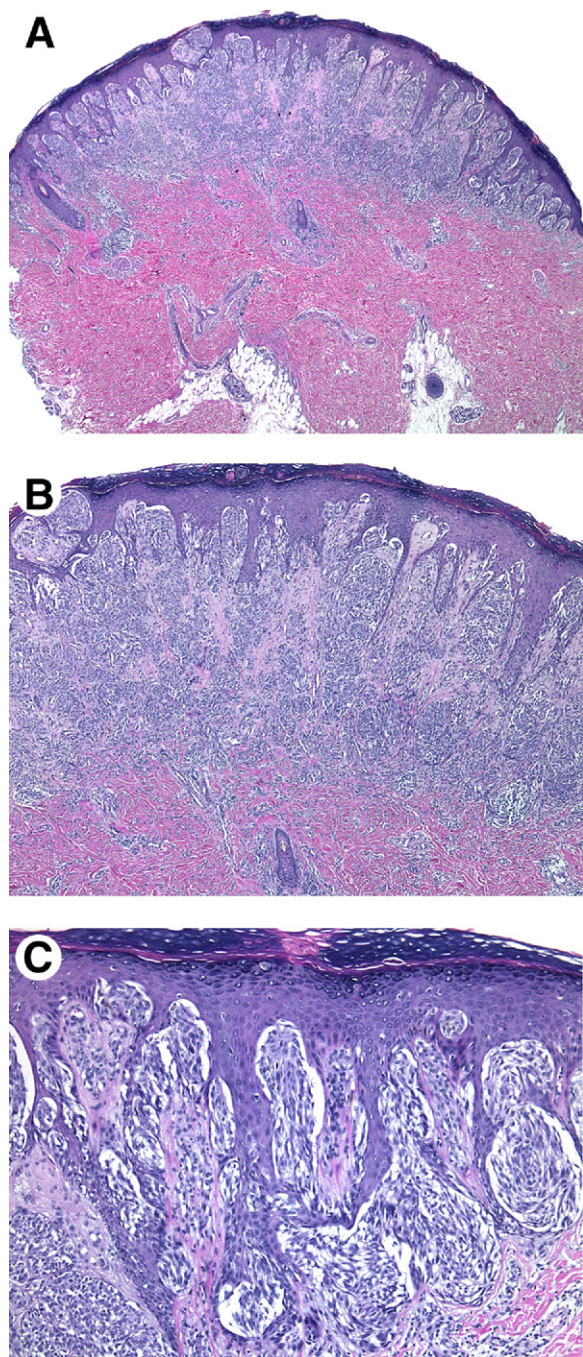


Figure 2 (A) Symmetric, well-circumscribed, wedge-shaped proliferation of melanocytes. (B) Large melanocytic nests with slight variation in size and shape are present in the epidermis. There is maturation of nests and melanocytes with progressive descent into the dermis. (C) Clefts are seen between the vertically oriented melanocytic nests and the adjacent epidermis.

bottom of the neoplasm, as well as inside melanocytic nests and cytoplasm of melanocytes.²⁵

A common feature in SN is the presence of dull-pink globular acellular structures composed of basement membrane material, named Kamino bodies (Fig. 3). They are often found within the epidermis above dermal papillae. Numerous Kamino bodies, especially if they are confluent and of

large size, are mostly seen in SN.²⁶ They are Periodic Acid-Schiff positive. The epidermis associated with SN is acanthotic, hyperplastic, with hypergranulosis and hyperkeratosis. Perfectly symmetric epidermal hyperplasia with expansion at the center and attenuation at the periphery is a feature of SN, whereas there is usually “consumption of the epidermis” in SMM. Lymphocytic inflammatory infiltrate is often seen around vessels and at the base of the lesion but not admixed with the melanocytes. Blood vessels might be dilated and prominent. Desmoplastic SN is a variant of SN composed of spindle or epithelioid cells embedded in a markedly fibrotic stroma (Figure 4A-C). Junctional component is absent. When the melanocytes are embedded in hyalinized collagenous paucicellular stroma, the term hyalinizing SN is used. Other variants of SN include angiomatoid, myxoid, plexiform, and rosette-like SN.⁵ Combined melanocytic nevi, containing a component of common melanocytic nevus, congenital nevus, and a blue or deep penetrating nevus, as well as an SN have been described.²⁷

From a histologic point of view there are only a few differences between SN in children and SN in adults according to the data of 2 more recent studies: Kapur et al²⁸ compared 27 features in specimens obtained from both age groups. They found that the only statistically significant difference was the greater number of intradermal lesions and increased dermal fibroplasia in SN from adult patients. Requena and colleagues found hyalinization to be the only histologic parameter of statistic significance more frequently encountered in adults than in children.²³

Atypical Spitzoid Neoplasm

ASN is a histopathologic concept; therefore, a distinct clinical presentation, much like that of SMM, has not been described. The term, ASN is used for lesions that do not precisely conform to the category of a “typical” SN but that do not fulfill the criteria for melanoma. Under this designation, which is not uniformly accepted and used among dermatopathologists, is a broad category of lesions also known as atypical Spitz tu-

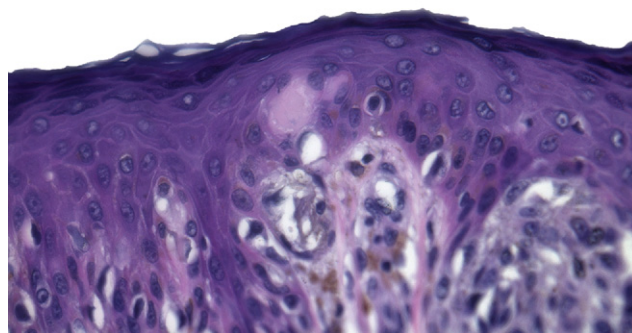


Figure 3 Kamino body as a dull-pink globule in the epidermis.

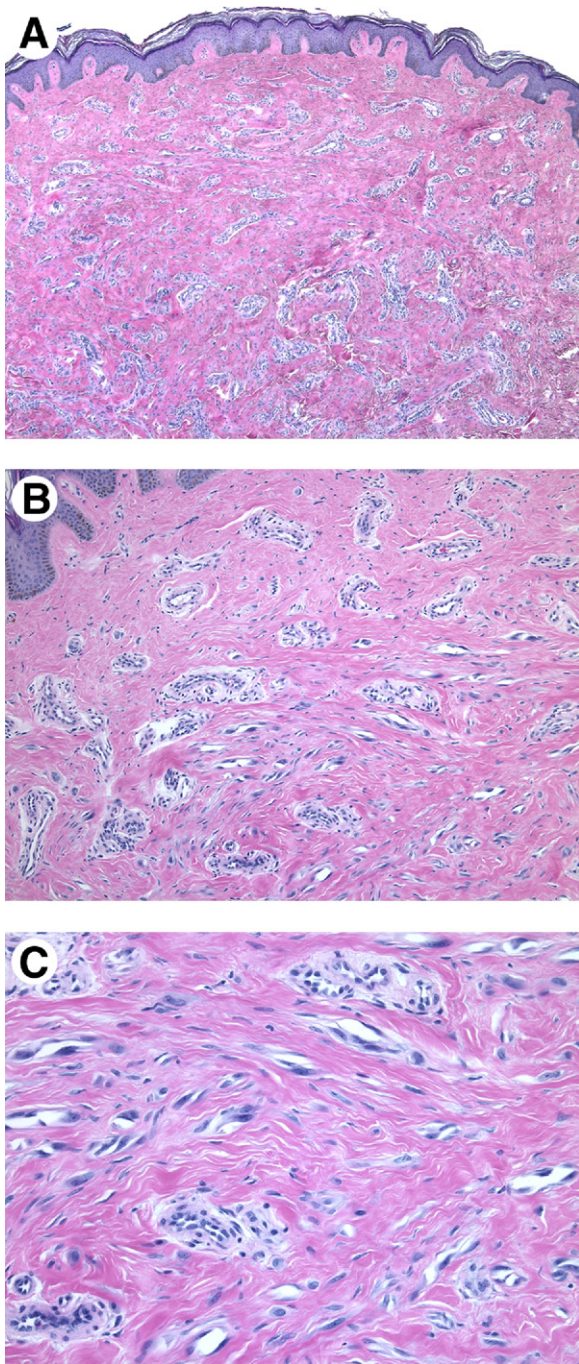


Figure 4 (A) Slightly dome-shaped lesion with prominent vessels, not easily recognized small nests and fascicles of melanocytes, and fibrotic stroma. (B) Small fascicles of melanocytes and single cells in between thickened collagen bundles. (C) Epithelioid and spindled melanocytes embedded in markedly fibrotic stroma.

mors or atypical Spitz nevi.²⁹ It is impossible to precisely define the histopathologic criteria for ASN, because this term is used to describe lesions with the architecture and cytomorphology of both SN and malignant melanoma, in which a firm histopathologic diagnosis of one or the other cannot be made with absolute certainty. This broad category includes SN with atypical features, which deviate from the stereotypical depiction of the classic SN. It also includes melanocytic

lesions that display conflicting histologic criteria, ie, some features of benign SN and other features of SMM. At the other end of the spectrum are melanocytic lesions that show many histologic features of melanoma. Because of the young age of the patients and the fact that malignant melanoma is rare in youngsters and SN is quite common, dermatopathologists are sometimes reluctant to make an unequivocal diagnosis of melanoma in children.

The term ASN was first introduced by Reed in 1975 to describe a Spitzoid lesion with densely cellular fascicles of spindled cells that compressed its stroma.³⁰ Barnhill and colleagues used the following criteria to characterize an ASN: significant deviation from those criteria conventionally ascribed to typical SN (while maintaining some of the customary criteria), for example size larger than 1 cm, ulceration, extension into deep dermis or subcutis, prominently increased cellularity or confluence of growth, intradermal mitoses, lack of maturation toward the base, significant nuclear pleomorphism, and aberrant or sheet-like dermal growth pattern.^{2,31} The presence and degree of variation of these features are weighed subjectively and individually, therefore considerable disagreement exists among both clinicians and dermatopathologists regarding the diagnosis and management of ASNs. It is not surprising that multiple studies have demonstrated great interobserver variability in the application and interpretation of histologic criteria in the evaluation of Spitzoid lesions even among expert dermatopathologists.^{2,32-37}

ASNs show architectural asymmetry, lack of circumscription, lack of maturation with descent in the dermis, nuclear and cellular pleomorphism, increased number of mitotic figures, increased cellularity and confluence of growth, deep mitotic figures, atypical mitoses, and, often, deep extension to the subcutaneous fat (Figure 5A-C).^{2,4,29} Features that may be helpful in the differential diagnosis between SN and SMM are symmetry or lack thereof, uniformity of nests from side to side, brisk mitotic rate, mitoses at the base, abnormal mitoses, Kamino bodies, ulceration, and pigment within melanocytes at the base. Many attempts have been made to better categorize ASNs into high-risk and low-risk lesions based on several histopathologic criteria. Among these are the presence of ulceration, large size (>1 cm), asymmetry, deep extension, hypercellularity, and brisk mitotic activity.^{25,26,38} In a method advocated by Spatz et al, a lesion that cannot be judged as clear-cut SN or SMM is evaluated and scored for lesional diameter, presence of ulceration, mitotic activity, deep extension into the fat, and other features. On the basis of their data from a collection of problematic cases,³⁹ a progressively greater score indicates a greater risk of metastases. Fat involvement, which correlates with tumor thickness, has been reported to be frequent in patients with metastatic evolution.^{2,40,41}

Other clues that may be helpful in the distinction between SN and SMM, when present, include solar elastosis in Spitzoid melanomas and extensive pagetoid spread of melanocytes in the epidermis, reaching its uppermost levels and lateral borders.

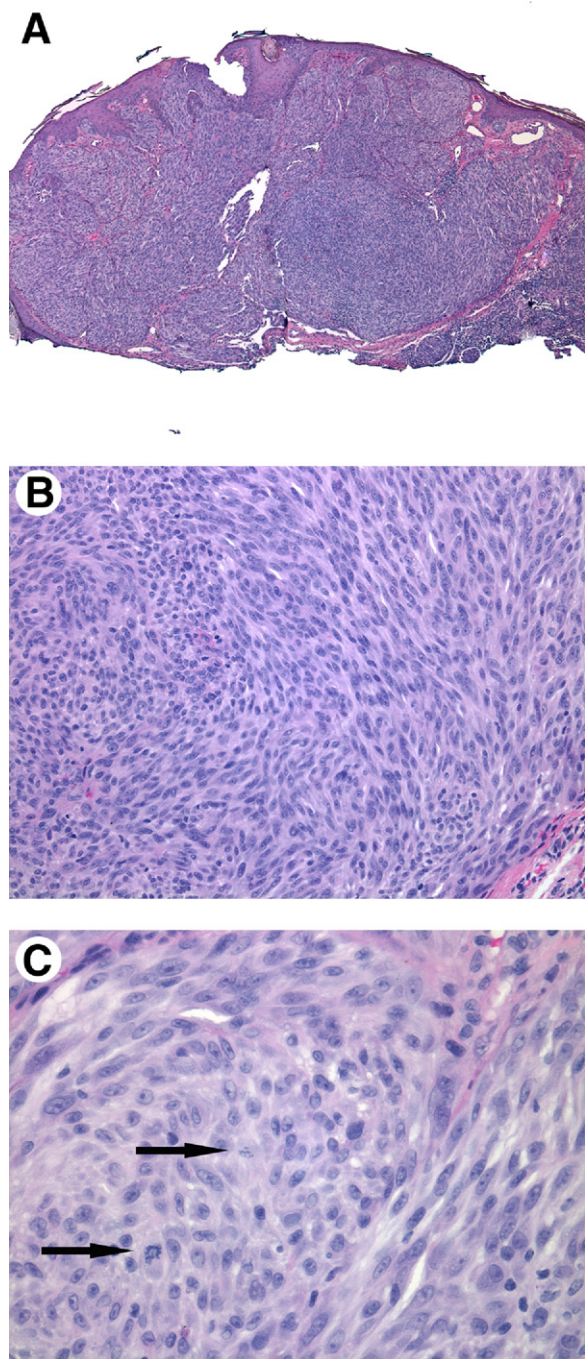


Figure 5 (A) Asymmetric and poorly circumscribed proliferation of melanocytes in the epidermis and confluent nests in the dermis. (B) Sheets of melanocytes with slight pleomorphism and nuclear hyperchromasia. (C) Two mitoses in a hypercellular area of this atypical Spitzoid neoplasm (arrows).

The similarities between an SN and an SMM are quite often so striking that if there is no solid argument for a specific diagnosis, these lesions are often qualified as ASNs, ie, placed in the “gray” zone. Interestingly, the age of the patient is often heavily relied upon and used as a criterion by dermatopathologists when approaching a borderline melanocytic lesion.^{42,43} The distinction between SN and SMM still remains one of the most important and challenging areas in pathol-

ogy. We are faced with the limitations of criteria-based analysis at this time. Although ASN have generally been reported to have a good prognosis, well documented cases of metastasis and death exist.^{2,31,44} For lesions in the “gray” zone, it is wise to admit the uncertainty and provide a differential diagnosis and microstaging attributes that would apply if the lesion were interpreted as a melanoma.⁴⁵ Because the malignant potential of these lesions is uncertain, many clinicians and patients make decisions to treat them as if they were melanomas with excision and, often, a sentinel lymph node biopsy (SLNB).⁴⁶

SMM is a malignant melanocytic lesion with architectural and cytologic features resembling those of an SN.⁴ Most SMMs develop in adulthood. However, they may occur in prepubescent children and adolescents. Approximately 2% of melanomas occur in patients younger than the age of 20 years. A total of 0.3% to 0.4% of these melanomas occur in prepubescent children and about one-third demonstrate Spitzoid characteristics.^{14,47-49} It should be noted that in very young patients (<1 or 2 years of age) striking cellular pleomorphism, occasional mitotic figures at the bottom, or a growth pattern in solid sheets are possible in lesions of benign outcome.²⁵ Cases of SMMs in this age group usually have a combination of striking atypia, mitoses, pleomorphism, solid sheets growth pattern, and involvement of the subcutis.^{29,38} It is imperative that the data from the microscopic examination of the lesion is always interpreted along with the clinical information, especially the age of the patient, location of the lesion, history of changes, symptoms, personal and family history of melanoma, etc.⁵

Ancillary Studies

Immunohistochemistry

A distinction between SN and SMM cannot be reliably made on the basis of a distinctive immunohistochemical staining pattern. However, these stains can be useful in distinguishing Spitzoid melanocytic lesions from nonmelanocytic lesions. Although there are some differences in staining patterns between SN and SMM, there is often overlap and sensitivity and specificity are not satisfactory. S100 and Mart-1/Melan A are diffusely expressed in both SN and SMMs.⁵⁰⁻⁵² In contrast, HMB-45 and tyrosinase diminish toward the base of SN.⁵²⁻⁵⁴

Immunohistochemical staining may be helpful for detection of mitoses to determine the proliferative activity of a lesion. The rate of staining with proliferation markers is generally lower in SN compared with SMM.^{51,55} Kapur and colleagues²⁸ studied Ki-67 nuclear staining and determined that it was lower in both typical SN and ASN than in malignant melanoma ($P < 0.001$). Cytoplasmic expression of fatty-acid synthase (a key enzyme responsible for the synthesis of fatty acids), has been shown to progressively increase in a gradient from SN to SMM.²⁸ p53 is not significantly expressed in SN, whereas there is high expression in melanoma.^{28,56,57}

CD133 (Prominin-1) is a cancer stem cell-associated marker with increased expression in the cancer stem cell fraction of a large variety of human malignancies, including

malignant melanoma.⁵⁸ Dhaybi and colleagues⁵⁹ studied the expression of CD133 in cases of malignant melanoma in children, most of which were Spitzoid, and SN in the same age group. Only 4 of the 12 patients with melanoma showed positive expression of CD133. These were the only 4 patients with metastases—3 had lymph node metastasis and 1 patient had multivisceral metastases. However, all SN were CD133 negative. Their results showed that CD133⁺ cancer stem cell expression in childhood malignant melanoma might correlate with lymph node and/or visceral metastasis. If further validation confirms CD133 cancer stem cell expression to be consistently negative in SN and consistently positive in childhood malignant melanomas, where it correlates with lymph node and/or visceral metastasis, this might shed some light in the gray zone of borderline melanocytic lesions. Furthermore, it may allow for prognosticating the biologic behavior of these lesions and for better clinical management.

Molecular Studies

Comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) are methods that can determine DNA copy number changes associated with certain types of melanocytic lesions and represent new tools in the assessment of difficult melanocytic proliferations of unknown malignant potential. Most SN reveal no genomic aberrations by CGH. A total of 20% to 25% of SN show an isolated gain of chromosome 11p, an anomaly that has not been documented in association with melanoma.⁶⁰ In contrast, more than 95% of melanomas show multiple chromosomal aberrations, including gains and losses.^{61,62} The advantage of CGH is that the entire genome is analyzed but the complexity of the assay restricts its application to specialized centers. FISH represents a more expeditious technique; however, the currently used probe set may hold lower sensitivity for the detection of childhood type Spitzoid melanoma in comparison with conventional (adult type) melanoma. Many SN do not show mutations in oncogenes. A minority of SN with 11p copy number increases have been found to have an HRAS mutation.⁶³ The presence of HRAS in the absence of other related oncogene mutations differs from the genetic signature of melanoma. The majority of melanomas have BRAF or NRAS mutations. By contrast, BRAF mutation has been found in a small subset of SN.⁶⁴ When SN and malignant melanomas were compared using both CGH and FISH for chromosomal aberrations, melanomas showed frequent deletions of 9p, 10q, 6q, and 8p, and frequent gains of 7, 8, 6p, and 1q.^{60,61,63} On the contrary, SN showed no or very limited chromosomal gains or losses.

CGH and FISH are promising ancillary tests; however, the sensitivity and specificity of those studies are not ideal, and there are many pitfalls, including false-positive and false-negative results. “Borderline” lesions often show “borderline” features at the cytogenetic level. Nevertheless, molecular studies are a potentially exciting advance in the diagnostic process of Spitzoid melanocytic lesions in the gray zone.

Management and Prognosis

Classic SN represent benign melanocytic lesions that have no potential for metastasis. Even if incompletely excised based on histologic examination, SN rarely persist.⁶⁵ However, some incompletely excised SN may recur within a few months to a few years.^{3,21} In a survey carried out to ascertain how dermatologists manage SN, the results showed that the vast majority of dermatologists (93%) recommend performing a biopsy on suspected SN, 43% recommend total biopsies and 55% recommend partial biopsies.⁶⁶ 69 percent of physicians would completely excise a lesion that was histologically diagnosed as an incompletely removed SN. 70 percent of general dermatologists and 80% of pediatric dermatologists would recommend excision with a 1-2-mm margin of normal-appearing skin around an SN. However, pigmented lesion-clinic directors favored total excision of all SN in adults. The recommendations at the pigmented lesion section of the Skin and Cancer Unit at New York University, where most patients are adults, are to completely excise all SN with surgical margins of 2 mm and have follow up visits.⁶⁷

Treatment for SMM is the same as that for conventional melanoma, with wide excision guided by the depth of the lesion, ancillary work-up, and nonsurgical treatment as deemed appropriate. Just as uncertainty exists concerning the nature and diagnosis of ASN, there is uncertainty concerning their management. How could one possibly have a treatment plan when one is not sure what to treat? Whenever the possibility of cancer is raised, it is a common reaction to address the worst possible scenario. Surgical options and adjuvant therapy are often chosen by the patients and their clinicians as if the patient had melanoma, including removal of the primary tumor and staging work up.

The uncertainty and difficulty in the morphologic classification and prediction of the biologic behavior of ASNs have led to the adoption of the SLNB as both a prognostic and, in some cases, helpful diagnostic adjunct in borderline cases.² The practice of categorizing a case of histologically ambiguous Spitz lesion as malignant based on the sentinel lymph node (SLN) positivity is increasingly adopted particularly among surgeons. Some authors believe that “a melanocytic neoplasm that metastasizes is melanoma.”^{29,68} Kelley and Cockerell⁶⁸ proposed in 2000 that, in addition to wide excision, SLNB might be considered for patients if their tumors, under the assumption they were melanomas, would make them eligible for this procedure. Under this concept, those patients who eventually turn out to have malignant melanoma would not have been denied an option they would have been offered had the melanoma been recognized earlier. The authors also suggested that the SLN procedure might provide an additional benefit. Its results may be of potential diagnostic value if there are metastatic tumor deposits in the SLN, which will support the malignant nature of the primary tumor. Therefore, SLNB is recommended by some authors for patients with ASNs of 1-mm thickness or more.⁶⁹ However, if we do not know the biologic behavior of ASNs that have positive SLN, how confident can we be to advocate a complete lymphadenectomy, which is a treatment of poten-

tial consequent morbidity for the patient? As Kwon et al⁷⁰ remarked on this subject, "Compounding uncertainty with more uncertainty is never a good idea." Conversely, what does a negative SLNB prove in an ASN? Absence of nodal metastasis does not exclude a malignant primary tumor, as metastasis from melanomas can be seen long after the diagnosis.

The issue becomes even more complicated by the fact that the presence of tissue types normally foreign to lymph nodes within a node does not necessarily equate metastatic malignancy. Benign leiomyomas in a lymph node and nodal melanocytic nevi have been reported.⁷¹ A number of criteria have been proposed to differentiate between benign nodal melanocytic nevus and metastatic malignant melanoma deposits based on the location of the melanocytes: nodal nevi tend to be present primarily in the fibrous capsule, whereas metastatic melanomas are usually found in the parenchyma. The melanocytes in nodal nevi are bland versus atypical and pleomorphic in melanomas, with mitoses and necrosis.⁶⁷ Immunohistochemical pattern of staining may also be helpful. Nodal nevi are negative or only focally positive for HMB-45 and negative for MIB-1, whereas metastases of malignant melanoma are either negative or positive for HMB-45 and positive for MIB-1.

There are many recent studies reporting the experience of different centers with SLNB for diagnostically problematic ASNs.^{46,67,72-76} Their results indicate that the number of patients with ASNs who undergo SLNB and have positive nodal melanocytic aggregates range from 29% to 50% with a mean of 39%. Except Breslow's depth there were no histologic or clinical features that distinguished the nodal positive from nodal negative groups.⁷⁰ The size of the nodal melanocytic aggregates ranged from 0.1 to 5.0 mm and their location included multiple foci: subcapsular areas, within the sinus, and/or within the parenchyma. To complicate matters further, there are reports in the literature of noncapsular location of nodal nevi.⁷² In the cases of ASNs with positive SLNBs, complete lymphadenectomy has typically revealed no additional nodal positivity and 2- to 3-year follow-up have shown no further disease recurrence.^{72,73}

A study of Ludgate and colleagues⁴⁶ concluded that patients with ASNs and positive SLNB were younger than those with negative SLNs. Although a significant number of patients with ASNs are found to have positive SLNs, the vast majority of them subsequently have an indolent clinical course quite different from what would be expected from conventional melanomas of similar thickness. How can one reconcile the presence of metastatic tumor deposits with a favorable clinical course? One fact worth considering is that most of the tumor deposits are small. Small tumor volume in the SLN has been associated with better prognosis even for conventional type melanoma. Furthermore, the smaller the tumor volume, the more difficult it is to distinguish nodal nevi from metastatic melanoma. Because there are no well-defined diagnostic criteria for ASNs and this is a category that encompasses a very wide range of lesions from SN with atypia to overt SMMs, such information cannot be uniformly accepted, as lesions classified as ASNs at 1 center may be diag-

nosed as SMM at others. Furthermore, the follow-up period in all available studies is less than 5 years, which is the widely accepted cut-off period for assessment of disease-free remission in cancer survivors.

In summary, there is much uncertainty related to SLN findings. The diagnosis is not clarified if the SLN is negative. If the SLN contains small deposits of melanocytes, the significance of these findings is unclear. Next comes the question whether the deposits represent a nodal nevus or metastatic melanoma. However, if there are large deposits of overtly malignant melanocytes with atypia, pleomorphism, numerous mitoses, including atypical ones, as well as areas of necrosis, these should be interpreted as metastatic melanoma.

If, however, there is still uncertainty about the correct diagnosis, further ancillary tests, such as FISH or CGH may be performed. If the tumor is found to lack any chromosomal aberrations or shows increase in the copy number of chromosome 11p, current evidence suggests that the chance of this lesion representing malignant melanoma is low and further management and care may be designed as for a patient with a probable nevus and not for melanoma.^{60,63} Complete excision of the lesion is recommended if it has not been completely removed initially and, in the authors' opinion, SLNB should not be performed in all such patients. If, by contrast, CGH or FISH reveal chromosomal aberrations typically associated with melanoma, further management as for melanoma is recommended. If an SLN is found to contain melanocytes of uncertain significance, the authors caution against proceeding with complete lymph node dissection, and that it may be in the best interest of the patient not to have any surgical intervention given the lack of proven survival benefit and the risk of iatrogenic morbidity.

The Authors' Recommendations for Management of ASNs

When assessing a Spitzoid melanocytic lesion, all attempts should be made to arrive at a definitive diagnosis of SN or SMM by careful microscopic examination and objective application of available criteria. If the diagnosis still remains uncertain and there are conflicting criteria, some of which favor a benign nevus, whereas others suggest melanoma, it might be a good idea to obtain a second opinion in search of the correct diagnosis. However, even experts frequently disagree and 1 lesion may be called an SN by 1 expert and SMM by another.

ASNs should be excised (with at least a 1-cm margin if one has made the decision to treat the lesion as if it were a melanoma) to ensure complete removal and to prevent local recurrence. Patients should be informed about the uncertainty of the diagnosis and treatment and management options should be discussed, including the option of treating the patient in the same manner one would for malignant melanoma. The patient should also be educated about the role of SLNBs. SLNB has been designed as a staging procedure for histologically unequivocal malignant melanoma and performing an SLNB in an ASN is not to settle the diagnostic

uncertainty. The results from an SLN can only be useful diagnostically if it contains frank malignant melanoma in large deposits.

If a positive SLNB shows a large tumor burden with effacement of the lymph node architecture, the lesion is considered more likely to be malignant and counseling regarding complete lymph node dissection and adjuvant therapy is advised. If the SLNB contains only a few microscopic deposits of intraparenchymal melanocytes with <1% lymph node surface area involvement, the question of proceeding with complete node dissection and adjuvant therapy remains controversial. Because benign Spitzoid proliferations are more common in children and adolescents compared with adults, the authors recommend an age-based approach in the management of a minimally involved SLN: (1) if the patient is 20 years or younger and has less than 1% of the lymph node involved, close observation of the regional nodal basin clinically is a reasonable option after extensive counseling. In addition, serial ultrasounds may be beneficial to monitor the nodal basin; (2) if the patient is older than 20 years and has less than 1% of the lymph node involved, observation remains an option, but a lower threshold for considering a complete node dissection should be maintained, given the higher incidence of melanoma in this population. In conclusion, Spitzoid melanocytic lesions ranging from SN, to ASNs, and SMMs remain intriguing and challenging even after more than half a century of their initial description in the literature.

Large, multicenter, long-term histologic, molecular, physical, and chemical diagnostic studies are necessary to establish reliable differences between SN and SMMs and place ASNs in either the benign or the malignant category, thus significantly decreasing the gray area. These studies should include clinical information and correlation with the ultimate goal to more accurately predict the prognosis and optimize the treatment protocols for Spitzoid neoplasms.

Currently, there are 5 Specialized Programs of Research Excellence in skin throughout the country, funded by the National Institutes of Health, to promote interdisciplinary research and move basic research findings from the laboratory to clinical settings. These include the University of Pittsburgh Cancer Institute, the University of Texas, MD Anderson Cancer Center in Houston, Yale University School of Medicine in New Haven, the Wistar Institute/University of Pennsylvania in Philadelphia, and the Dana Farber/Harvard Cancer Center in Boston. The main focus of their projects is melanoma. Another step in this direction is the establishment of the "Spitzoid Neoplasm Repository" at Yale University, which is a compilation of tissue samples and data on a large number of patients with Spitzoid lesions. The recently founded International Spitzoid Neoplasm Study Group will allow pathologists and dermatologists to work together, join forces, collaborate, study, and share information and ideas to better research and classify Spitzoid neoplasms.

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