Classic and Atypical Spitz Nevi: Review of the Literature

LT Daryl J. Sulit, MC, USN; LCDR Robert A. Guardiano, MC, USN; COL Stephen Krivda, MC, USA

GOAL

To understand classic and atypical Spitz nevi to better manage patients with these lesions

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the clinical and histologic features of the classic Spitz nevus.
2. Recognize the clinical and histologic features of the atypical Spitz nevus.
3. Discuss the treatment options for patients with classic and atypical Spitz nevi.

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Both classic and atypical Spitz nevi are uncommon melanocytic lesions usually presenting in children and adolescents. The classic Spitz nevus typically is benign and has characteristic clinical and histologic features. In contrast, the atypical Spitz nevus has an unknown clinical prognosis, and its clinical and histologic traits are loosely defined. Melanoma can have similar features to both classic and atypical Spitz nevi and must be ruled out in all cases. We review the literature on classic and atypical Spitz nevi, advances in differentiating both types of nevi from melanoma, and treatment options.

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Dr. Sulit is a dermatology resident from the Department of Dermatology, Naval Medical Center, San Diego, California.
Dr. Guardiano is Assistant Professor of Dermatology, Uniformed Services University of the Health Sciences, Bethesda, Maryland.
Dr. Krivda is Department Head, Dermatology Department, National Naval Medical Center, Bethesda, and Chief, Dermatology Service, Walter Reed Army Medical Center, Washington, DC.

Spitz nevi were first described in 1948.[1] Spitz[1] originally called these lesions *benign juvenile melanoma*. She was able to identify and describe a separate class of benign melanocytic neoplasms in children that were previously diagnosed and treated as melanoma.[2] Prior to this discovery, the standard of care was to remove all suspicious pigmented lesions in

children prior to adulthood to prevent possible malignant transformation.[2,3] Today, *Spitz nevus* is the more commonly used term for benign juvenile melanoma because it is encountered occasionally in adults and the term *melanoma* carries a negative connotation.[4] Other synonyms include juvenile melanoma, Spitz tumor, nevus of large spindle and/or epithelioid cells, and spindle cell and epithelioid nevus.[3,5]

Classic Spitz Nevus

Spitz nevi are uncommon. The approximate incidence is 7 per 100,000 people. Spitz nevi are more frequently found in children and adolescents but can occur in adults.[6,7] Spitz nevi occur predominantly in the white population and slightly more often in females.[4,8]

A Spitz nevus can arise de novo or in association with an existing melanocytic nevus. The lesions can be asymptomatic or have a history of rapid but limited growth. Clinical features of Spitz nevi are well-circumscribed, symmetrical, small- to medium-sized firm papules with smooth discrete borders and a uniform color (typically pink or flesh colored).[9] Spitz nevi can occur in various shapes. In a study of 211 cases of Spitz nevi, 19% were described as flat or uneven, 24% as polypoid, and 57% as plateau or elevated.[7] Spitz nevi usually are found on the face, neck, or lower extremities but can occur anywhere on the body.[7,9] Size is typically less than 6 mm (Figures 1 and 2).

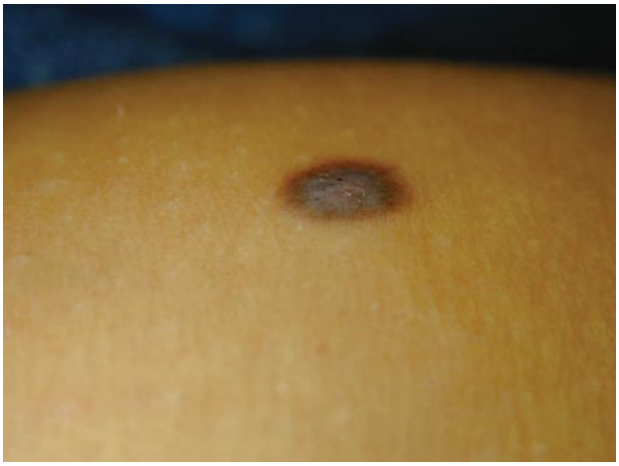

Figure 1. Classic Spitz nevus on the leg of a child. A 6-mm hyperpigmented, well-defined, dome-shaped, firm papule. Photograph courtesy of Dr. Mark Blair.

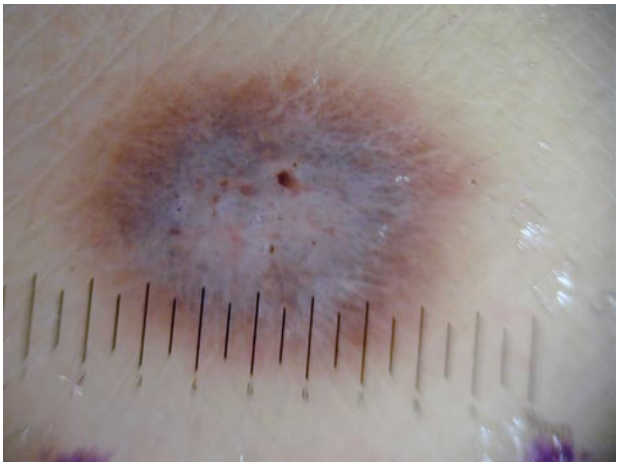

Figure 2. Classic Spitz nevus (size, 6 mm) examined with dermatoscopy. Photograph courtesy of Dr. Mark Blair.

The classic Spitz nevus histologically consists of large spindle and/or epithelioid melanocytes arrayed as epidermal nests grouped in a vertical orientation (called "bunches of bananas" or "raining down pattern"), with clefting artifact at the perimeter (Figure 3).[4,9,10] The nests are fairly uniform, nonconfluent, and evenly spaced. There is little or no pagetoid spread pattern. Epidermal changes include acanthosis, hypergranulosis, and hyperkeratosis. The intradermal pattern displays maturation, with single-file or single-unit arrays descending to the base. Eosinophilic Kamino bodies frequently are found along the dermoepidermal interface. Kamino bodies are globular clusters that represent apoptotic degenerative melanocytes (Figure 4). They stain positive with both periodic acid-Schiff and trichrome stains. At the dermal base, there is no mitosis, no pushing deep margins, and lack of significant pleomorphism. Little or no melanin is present.[4,9,10] The classic Spitz nevus behaves in a benign manner.[1] The differential diagnosis of the Spitz nevus includes pyogenic granuloma, mastocytoma, juvenile xanthogranuloma, and malignant melanoma.

Atypical Spitz Nevus

The atypical Spitz nevus is difficult to formally define. Instead, it is loosely defined. An atypical Spitz nevus shares histologic features with the classic Spitz nevus, but it may have one or more atypical features, which can be characteristic of malignancy.[10-12] Gross atypical features may include irregular shape, nonuniform color, large size, or ulcerations. Histologically, there can be one or more of the following features: pleomorphism; increased cellularity; loss of cellular cohesion; epidermal pagetoid spread; minimal epidermal changes; absence of Kamino bodies; lack of maturation in the intradermal pattern; high-grade nuclear atypia; high basal mitotic rate; pushing deep margins into the dermal base or subcutis; and nests variable in size, shape, and orientation.[9,10,13]

The behavior of any atypical Spitz nevus is unpredictable. There are case reports of metastasizing and malignant lesions with Spitz-like

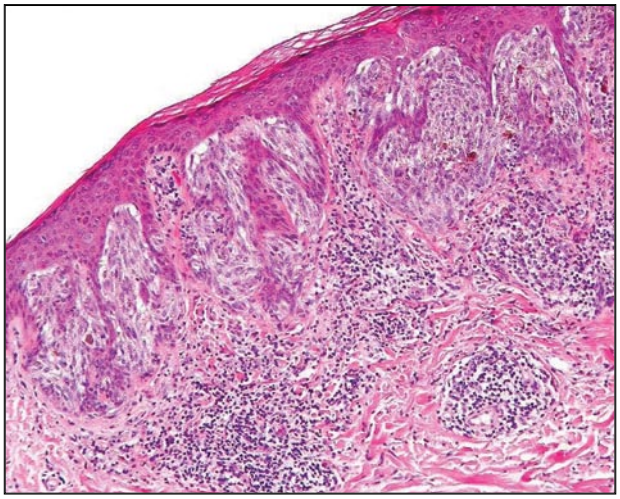

Figure 3. Classic Spitz nevus showing epidermal nests grouped in a vertical orientation, the so-called bunches of bananas (H&E, original magnification ×10).

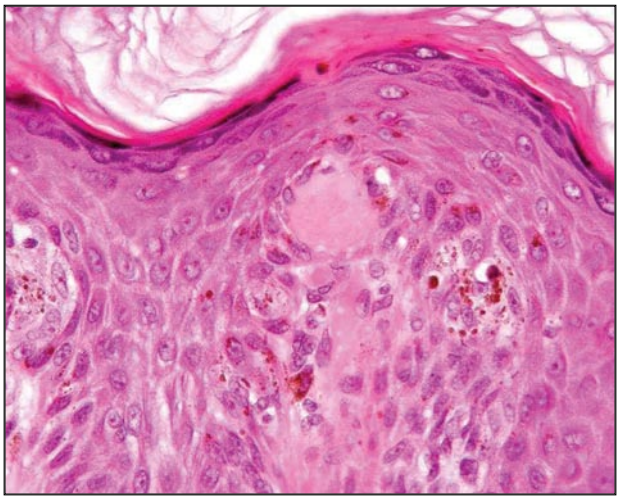

Figure 4. Classic Spitz nevus. At the upper right corner is an amorphous globular-shaped Kamino body along the dermoepidermal interface (H&E, original magnification ×40).

characteristics causing fatal outcomes.[11,13] However, there also are studies that show Spitz nevi acting in a benign manner, even with a history of metastases.[11,13-15] Some researchers try to explain this phenomenon by theorizing that Spitz nevi and melanoma exist along a continuum with the classic benign Spitz nevus at one end of the spectrum and the aggressive malignant melanoma at the opposite end, with a diverse range of atypical Spitz-like lesions with features of both in between.[4,10-12,14] Other researchers refute this claim and view the unequivocal Spitz nevus as benign and unrelated to melanoma. They point out that many of these case reports of melanomas with Spitz-like features do not fit the diagnosis of the Spitz nevus.[16]

In general, the more features an atypical Spitz nevus shares with melanoma, the greater the risk for malignant behavior. In 1999, Spatz et al[12] proposed formal and specific criteria for determining the risk for malignant behavior in atypical Spitz nevi in children. In the retrospective study, atypical features were used to define atypical Spitz nevi and grade their risk for metastasis. The 5 major factors were age, size, presence of ulceration, involvement of subcutaneous fat, and mitotic activity. Positive risk factors that increased the grade included age greater than 10 years, diameter greater than 10.0 mm, lesions with fat involvement, presence of ulceration, and dermal component mitotic activity greater than 5 mitoses/mm^2. The higher the grade, the higher the risk for malignancy and metastasis.[12] Since its publication, this grading system for categorizing atypical Spitz nevi has been put to use in a few case reports and studies.[17,18] Additional prospective studies using these criteria will be helpful in determining the true clinical nature of atypical Spitz nevi in children, the usefulness of this grading system, and the possible application of this grading system in adults.

Problems Differentiating Classic and Atypical Spitz Nevi From Melanoma

Melanoma is a major part of the differential diagnosis of Spitz nevi. The classic Spitz nevus typically has a benign nature, while the atypical Spitz nevus displays unpredictable behavior that appears to be dependent on the degree of atypia.[1,3,16] In contrast, melanoma is potentially fatal. Fortunately, Spitz nevi typically occur in children and the risk for having childhood melanoma is rare.[6,8,19] Though risk is minimal, rare cases of melanoma have been reported in children.[8,11,14,15,19-21] Therefore, making a correct diagnosis and ruling out melanoma is important.

Unfortunately, even with clinical and histologic guidelines, sometimes it is difficult to distinguish classic and atypical Spitz nevi from melanoma. The major problem is histologic overlap with Spitz nevi and melanoma. Many researchers have emphasized that there is no single discriminating factor for Spitz nevi and melanoma because virtually every trait of Spitz nevi has been described in melanoma.[2,10,13,20,22,23] Results of multiple studies show variability among researchers on the analysis of melanocytic nevi and melanoma lesions, and the final diagnosis was subjective.[5,22] In one retrospective study where clinical outcome was already known, 30 melanocytic lesions were evaluated independently by a panel of 10 dermatopathologists and categorized as either a typical Spitz nevus, atypical Spitz nevus,

melanoma, tumor with unknown biologic potential, or other melanocytic lesion.[5] The dermatopathologists were blinded to the clinical data. Evaluation of 17 Spitzoid lesions yielded no clear diagnostic consensus and a few lethal lesions were identified by most dermatopathologists as either typical or atypical Spitz nevi. The authors maintain that these results show that current objective criteria are deficient and inadequate to permit the discrimination of Spitz nevi with atypical features from melanoma.[5]

Given these histologic analysis limitations, many investigators are researching other tools and techniques that may help enhance diagnostic accuracy. Promising genetic analysis techniques include comparative genomic hybridization and fluorescent in situ hybridization.[24] In one study,[24] researchers compared Spitz nevi with primary cutaneous melanomas using comparative genomic hybridization and fluorescent in situ hybridization and discovered differences. In the study, Spitz nevi were found to have no chromosomal aberrations or gains in chromosome 11p or 7q21qter. In comparison, primary cutaneous melanomas had frequent chromosome deletions of chromosomes 9p, 10q, 6q, and 8p, and gains of chromosomes 7, 8, 6p, and 1q.[24,25] Immunohistochemistry is another potential tool for improving diagnostic accuracy. Examples of promising immunohistochemical markers include antibody MIB-1,[26-28] BCL-2,[29] and anti-S100A6.[30] Studies have shown that most melanomas are immunoreactive to MIB-1 and BCL-2, whereas Spitz nevi are not.[26-29] Recently, anti-S100A6 protein also was shown to be a potential immunohistochemical marker to differentiate a Spitz nevus from melanoma.[30] Anti-S100A6 is different from anti-S100 because it is more specific to a subclass of normal cell types and certain cancer cell lines. Investigators found strong, uniform, and diffuse S100A6 protein expression in the junctional and dermal components of all 42 Spitz nevi they studied versus weak and patchy S100A6 protein expression found mainly in the dermal component of 35 of 105 melanoma specimens they studied.[30] Although these techniques show exceptional potential, further research will be required to prove their reliability.

Management of Classic and Atypical Spitz Nevi

There is controversy regarding the treatment of a classic Spitz nevus. Some investigators recommend conservative treatment because a Spitz nevus is benign. They find that the Spitz nevus may be removed or left alone.[3] Others agree but would add that complete excision with clinical follow-up is appropriate if there are atypical features found on the Spitz nevus.[16,23,31] Other investigators are more aggressive and recommend complete excision with clear margins of all Spitz nevi, unequivocal or not, because Spitz nevi have histologic overlap with melanoma, and recurrent lesions may present with pseudomelanomatous changes, which makes differentiation more difficult later.[4,32] They conclude that the benefits of complete excision outweigh the risks of partial treatment.[4] Regardless of how a Spitz nevus case is managed, regular follow-up with a dermatologist is recommended to look for any changes or recurrences suggestive of malignancy.

Currently, there are no available evidence-based recommendations with predictive value for the specific management of atypical Spitz nevi because their clinical course is mostly unknown and unpredictable. Most articles that do address the management of atypical Spitz nevi state that they should be completely excised and followed periodically.[11,33] Murphy et al[34] suggest that an atypical Spitz nevus should be completely excised to avoid the rare possibility of a melanoma masquerading as an atypical Spitz nevus. Furthermore, if the physician is suspicious of malignancy, it is recommended that the lesion be managed like a melanoma and be removed in accordance with current melanoma margin guidelines or with comprehensive margin control via Mohs micrographic surgery.[34,35] Gurbuz et al[17] stated that surgical margin excision, sentinel lymph node dissection, and clinical follow-up is recommended for atypical Spitz tumors. However, currently there are no prospective studies that have tested these various recommendations on atypical Spitz nevi management.

Within the last few years, sentinel lymph node biopsy (SLNB) has been proposed as a useful tool in the management of melanocytic neoplasms of uncertain behavior, such as the atypical Spitz nevus.[36] Researchers recommend SLNB in atypical Spitz nevi greater than 1.0-mm thick.[18,36,37] Supporters maintain that it increases the sensitivity of the diagnosis of melanoma (vs atypical Spitz nevus) and identifies patients who may potentially benefit from early lymph node dissection and/or adjuvant therapy. They state that a positive SLNB supports the diagnosis of malignancy and recommend that the lesion be treated aggressively. If the SLNB is negative, melanoma cannot be completely ruled out, but there is more reassurance that the lesion may be confined to the skin and can be completely removed by excision.[18,36,37] Other advantages of SLNB include minimal invasiveness and morbidity. Some researchers believe melanocytic neoplasms in which melanoma cannot be ruled out should

undergo complete surgical excision with wide margins in accordance with current melanoma guidelines,[34,35] which can be as much as 3 cm.[36,38] A negative SLNB offers the advantage of planning a complete excision of an atypical Spitz nevus that preserves surrounding margins and is cosmetically more acceptable,[36] and avoiding the morbidity (ie, lymphedema, paresthesia) associated with regional or elective lymph node dissection.[18]

However, some researchers argue that a positive SLNB in an atypical Spitz nevus is not metastatic melanoma and point out articles that have shown classic and atypical Spitz nevi spreading to lymphatic vessels and lymph nodes but behaving in a benign manner.[11,13,15,21,37] Therefore, more studies are needed to assess the prognostic significance of positive SLNB in atypical Spitz nevi.[18]

REFERENCES

1. Spitz S. Melanomas of childhood. *Am J Pathol.* 1948;24:591-609.
2. Spatz A, Barnhill RL. The Spitz tumor 50 years later: revisiting a landmark contribution and unresolved controversy. *J Am Acad Dermatol.* 1999;40:223-228.
3. Paniago-Pereira C, Maize JC, Ackerman AB. Nevus of large spindle and/or epithelioid cells (Spitz's nevus). *Arch Dermatol.* 1978;114:1811-1823.
4. Casso EM, Grin-Jorgensen CM, Grant-Kels JM. Spitz nevi. *J Am Acad Dermatol.* 1992;27:901-913.
5. Barnhill RL, Argenyi ZB, From L, et al. Atypical Spitz nevi/tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. *Hum Pathol.* 1999;30:513-520.
6. Herreid PA, Shapiro PE. Age distribution of Spitz nevus vs malignant melanoma. *Arch Dermatol.* 1996;132: 352-353.
7. Weedon D, Little JH. Spindle and epithelioid cell nevi in children and adults. a review of 211 cases of the Spitz nevus. *Cancer.* 1977;40:217-225.
8. Bader JL, Li FP, Olmstead PM, et al. Childhood malignant melanoma. incidence and etiology. *Am J Pediatr Hematol Oncol.* 1985;7:341-345.
9. Elder DE, Murphy GF. Melanocytic tumors of the skin. In: Elder DE, Murphy GF, eds. *Atlas of Tumor Pathology*. Washington, DC: Armed Forces Institute of Pathology; 1990:40-57.
10. Piepkorn M. On the nature of histologic observations: the case of the Spitz nevus. *J Am Acad Dermatol.* 1995;32:248-254.
11. Barnhill RL, Flotte TJ, Fleischli M, et al. Cutaneous melanoma and atypical Spitz tumors in childhood. *Cancer.* 1995;76:1833-1845.
12. Spatz A, Calonje E, Handfield-Jones S, et al. Spitz tumors in children: a grading system for risk stratification. *Arch Dermatol.* 1999;135:282-285.
13. Smith KJ, Barrett TL, Skelton HG 3rd, et al. Spindle cell and epithelioid cell nevi with atypia and metastasis (malignant Spitz nevus). *Am J Surg Pathol.* 1989;13:931-939.
14. Barnhill RL. Childhood melanoma. *Semin Diagn Pathol.* 1998;15:189-194.
15. Melnik MK, Urdaneta LF, Al-Jurf AS, et al. Malignant melanoma in childhood and adolescence. *Am Surg.* 1986;52:142-147.
16. Shapiro PE. Spitz nevi. *J Am Acad Dermatol.* 1993;29: 667-668.
17. Gurbuz Y, Apaydin R, Muezzinoglu B, et al. A current dilemma in histopathology: atypical spitz tumor or Spitzoid melanoma? *Pediatr Dermatol.* 2002;19:99-102.
18. Lohmann CM, Coit DG, Brady MS, et al. Sentinel lymph node biopsy in patients with diagnostically controversial spitzoid melanocytic tumors. *Am J Surg Pathol.* 2002;26:47-55.
19. Handfield-Jones SE, Smith NP. Malignant melanoma in childhood. *Br J Dermatol.* 1996;134:607-616.
20. Crotty KA, McCarthy SW, Palmer AA, et al. Malignant melanoma in childhood: a clinicopathologic study of 13 cases and comparison with Spitz nevi. *World J Surg.* 1992;16:179-185.
21. Lerman RI, Murray D, O'Hara JM, et al. Malignant melanoma of childhood. a clinicopathologic study and a report of 12 cases. *Cancer.* 1970;25:436-449.
22. Farmer ER, Gonin R, Hanna MP. Discordance in the histopathologic diagnosis of melanoma and melanocytic nevi between expert pathologists. *Hum Pathol.* 1996;27:528-531.
23. Shimek CM, Golitz LE. The golden anniversary of the Spitz nevus. *Arch Dermatol.* 1999;135:333-335.
24. Bastian BC, Wesselmann U, Pinkel D, et al. Molecular cytogenetic analysis of Spitz nevi shows clear differences to melanoma. *J Invest Dermatol.* 1999;113:1065-1069.
25. Bastian BC, LeBoit PE, Hamm H, et al. Chromosomal gains and losses in primary cutaneous melanomas detected by comparative genomic hybridization. *Cancer Res.* 1998;58:2170-2175.
26. Bergman R, Malkin L, Sabo E, et al. MIB-1 monoclonal antibody to determine proliferative activity of Ki-67 antigen as an adjunct to the histopathologic differential diagnosis of Spitz nevi. *J Am Acad Dermatol.* 2001;44:500-504.
27. Li LX, Crotty KA, McCarthy SW, et al. A zonal comparison of MIB1-Ki67 immunoreactivity in benign and malignant melanocytic lesions. *Am J Dermatopathol.* 2000;22:489-495.
28. McNutt NS, Urmacher C, Hakimian J, et al. Nevoid malignant melanoma: morphologic patterns and immunohistochemical reactivity. *J Cutan Pathol.* 1995;22: 502-517.
29. Kanter-Lewensohn L, Hedblad MA, Wejde J, et al. Immunohistochemical markers for distinguishing Spitz nevi from malignant melanomas. *Mod Pathol.* 1997;10:917-920.

30. Ribé A, McNutt NS. S100A6 protein expression is different in spitz nevi and melanomas. *Mod Pathol*. 2003;16:505-511.
31. Kaye VN, Dehner LP. Spindle and epithelioid cell nevus (Spitz nevus). natural history following biopsy. *Arch Dermatol*. 1990;126:1581-1583.
32. Omura EF, Kheir SM. Recurrent Spitz's nevus. *Am J Dermatopathol*. 1984;6(suppl):207-212.
33. Zaenglein AL, Heintz P, Kamino H, et al. Congenital Spitz nevus clinically mimicking melanoma. *J Am Acad Dermatol*. 2002;47:441-444.
34. Murphy ME, Boyer JD, Stashower ME, et al. The surgical management of Spitz nevi. *Dermatol Surg*. 2002;28:1065-1069.
35. Zitelli JA, Brown C, Hanusa BH. Mohs micrographic surgery for the treatment of primary cutaneous melanoma. *J Am Acad Dermatol*. 1997;37:236-245.
36. Kelley SW, Cockerell CJ. Sentinel lymph node biopsy as an adjunct to management of histologically difficult to diagnose melanocytic lesions: a proposal. *J Am Acad Dermatol*. 2000;42:527-530.
37. Su LD, Fullen DR, Sondak VK, et al. Sentinel lymph node biopsy for patients with problematic spitzoid melanocytic lesions: a report on 18 patients. *Cancer*. 2003;97:499-507.
38. Martinez JC, Otley CC. The management of melanoma and nonmelanoma skin cancer: a review for the primary care physician. *Mayo Clin Proc*. 2001;76:1253-1265.