Interpretation of the Complex Melanoma Pathology Report

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KEYWORDS

- Atypical melanocytic proliferations • Melanoma • Melanocytic nevus
- Molecular dermatopathology

KEY POINTS

- The varying classifications of ambiguous melanocytic lesions are reviewed.
- When pathologic ambiguity has significant clinical relevance, discussion between the surgeon and a dermatopathologist can guide the appropriate treatment.
- Additional testing, such as immunohistochemistry, comparative genomic hybridization, fluorescence in situ hybridization, and/or genetic analysis may aid in challenging cases.

INTRODUCTION

We have a sound understanding of the diagnosis, natural history, and treatment of both benign pigmented skin lesions and melanoma.[1–3] However, there are various pigmented skin lesions that bear a gross and histologic resemblance to melanoma or melanocytic nevi, but are neither clearly malignant nor benign. The incidence of these cutaneous lesions—collectively called atypical melanocytic proliferations—is not known, partly because a histopathologic diagnosis code does not yet exist to identify them. Although the incidence remains undetermined, these lesions are not uncommon in practice, provoking significant anxiety for patients and posing a substantial diagnostic and therapeutic challenge to surgeons.

First, the pathologist may struggle to find features of a lesion that can be reliably used to identify it. Some histologic characteristics (such as symmetric silhouette) may be consistent with a nevus, whereas other features (such as mitoses or atypia) within the same lesion are worrisome for melanoma. This leads to ambiguity in the

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diagnosis and disagreement among pathologists when interpreting a biopsy specimen. Ultimately, some pathologists may merely report a diagnostic dilemma, not a diagnosis. Second, without a clear approach to identifying and characterizing these lesions, study of their natural history is highly problematic and indications for treatment remain uncertain.

The absence of a clear diagnosis, of course, does not relieve surgeons of the need to treat patients who come to clinic with an ambiguous pathology report. The therapeutic implications of our poor understanding of the natural history of atypical melanocytic proliferations is the possibility of overtreatment of lesions that pose no risk of harm and undertreatment of lesions that have real malignant potential. Here, we review the nomenclature, classification, and natural history of atypical pigmented cutaneous lesions to help the surgeon navigate the complex diagnostic and treatment approach required of these lesions. We focus our review on the basics of cytogenetic studies and mutational analyses that have clinical application for melanocytic tumors and discuss pitfalls in their interpretation.

NOMENCLATURE AND CLASSIFICATION

The nomenclature of various kinds of atypical melanocytic proliferations is as muddled as one might expect from a spectrum of pathologic entities that are poorly understood. Names frequently reflect the ambiguity: “minimal deviation melanoma,” “borderline melanocytic tumor,” “prognostically indeterminate melanocytic tumor,” “atypical blue melanocytic neoplasms,” “atypical Spitz tumor,” “atypical spitzoid melanocytic tumor,” and “atypical Spitz tumor of uncertain malignant potential.”[4–9] The inconsistency and imprecision of diagnostic terms can vary between institutions, and imprecise descriptions do little to guide consistent and appropriate treatment.

To address this, there have been attempts to formalize ambiguous diagnostic terms for atypical melanocytic proliferations with the goal of standardizing reporting and simplifying treatment—the most notable 2 efforts being the World Health Organization classification of melanocytic tumors of the skin and the second being the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx). The MPATH-Dx includes 7 categories based on histologic criteria and consensus on therapeutic approach. Most of the atypical melanocytic proliferations are included in the “variable classification” group comprising class 2, class 3, and class 4. When applied by expert dermatopathologists the reported consensus ranges from 64% for class 2 lesions to 84% for class 3 lesions (50), highlighting the difficulty of reaching a consensus on diagnoses for lesions in the variable classification group.[10]

Until a more reliable classification system is developed and validated, a clinically relevant way to broadly classify the various terms describing melanocytic proliferations is simply whether the lesion is confined to the epidermis versus lesions with a dermal component. Lesions that are largely confined to the epidermis include atypical intraepidermal melanocytic proliferation (AIMP),[9,11–14] intraepidermal borderline melanocytic tumor (intraepidermal BMT),[13–21] and superficial atypical melanocytic proliferations of uncertain significance (SAMPUS).[22–26]

As discussed below, dermal lesions are associated with increased risk of melanoma, distant metastases, and melanoma-specific death. The grouping of melanocytic lesions that have a dermal component include dermal borderline melanocytic tumor (dermal BMT) and melanocytic tumors of uncertain malignant potential (MELTUMP)[22–26] (see **Table 1** for a summary of diagnostic terms).

Table 1
Diagnostic terms of atypical melanocytic proliferations

Diagnostic Term	Acronym	Description
Atypical intraepidermal melanocytic proliferation	AIMP	High-grade melanocytic dysplasia confined to epidermis
Superficial atypical melanocytic proliferations of uncertain significance	SAMPUS	High-grade melanocytic dysplasia confined to epidermis
De novo intraepidermal melanocytic dysplasia	DNIEMD	High-grade melanocytic dysplasia confined to epidermis, possible precursor to melanoma in situ
Pagetoid melanocytic proliferation	PMP	Atypical melanocytes (single or nested) throughout epidermis, including granular layer
Minimal deviation melanoma	MDM	Resembles acquired or Spitz nevi, but with vertical growth phase and has cellular atypia, such as melanoma
Intraepidermal borderline melanocytic tumor	Intraepidermal BMT	Atypical melanocytic lesion confined to epidermis
Dermal borderline melanocytic tumor	Dermal BMT	Atypical melanocytic lesion with thick dermal component
Atypical junctional melanocytic hyperplasia	AJMH	Melanocytes with more atypia than dysplastic nevi, but less than melanoma in situ
Melanocytic tumors of uncertain malignant potential	MELTUMP	Atypical melanocytes with thick dermal component

DIAGNOSIS AND INTERPRETATION OF THE PATHOLOGY REPORT

There are many things to consider when reading a pathology report to help inform treatment recommendations for cutaneous melanocytic proliferations. Because most diagnoses of melanocytic lesions are made by the morphologic evaluation of a biopsy specimen, the type and adequacy of the biopsy must be assessed. An adequate specimen must be taken to avoid sampling error, but there is an increasing trend toward smaller or more superficial biopsies. False-negative rates of melanoma initially diagnosed as melanoma in situ have been reported as high as 12% to 16%.[27,28]

Second, a pathology report of melanocytic lesions (that are not clearly melanoma) will not necessarily remark on Breslow depth or Clark's level, but the depth of the lesion—whether it involves the dermis or is limited to the epidermis—is important to note because it correlates with likelihood of distal or local recurrence.

Third, terms are occasionally used that are not pathologic diagnoses per se, but rather histologic descriptions when the diagnosis is uncertain. In this case, the pathologist is alerting the clinician to a diagnostic dilemma, not a diagnosis. This can

happen, for example, when the pathologist is unable to exclude melanoma in situ because of the inadequacy of tissue or when there is no clinical knowledge of the lesion, such as size or appearance. There are also histologic features that can resemble melanocytic dysplasia concerning for melanoma in situ, but may arise because of inflammation or external trauma. One of the most common descriptors is AIMP. It is important for the surgeon to recognize when the pathologist is using a descriptive term, such as AIMP, because this may prompt the surgeon to either discuss the case further with the pathologist or ask for an opinion from another dermatopathologist. In the event that no consensus is reached and diagnostic uncertainly remains, there are ancillary diagnostic assays that may be requested to help clarify the diagnosis.

There are several assays that are in development to help shed light on the ambiguity of atypical melanocytic proliferations. Although staining with hematoxylin and eosin remains the gold standard in evaluating melanocytic lesions, emerging ancillary techniques are useful in cases of equivocal findings with conventional light microscopy. There are 4 categories of assays—immunohistochemistry, fluorescent in situ hybridization, cytogenetic studies, such as comparative genomic hybridization, and mutational analysis, such as gene expression assays—that are potential adjunctive tools to increase diagnostic accuracy (**Table 2**).

Immunohistochemistry

Basics

Immunohistochemistry is a microscopy-based technique and has been the primary adjunctive diagnostic tool to distinguish benign and malignant melanocytic tumors. The technique relies on labeled polyclonal or monoclonal antibodies that are specific for antigens of malignant cells not found on their benign counterparts.

Clinical applications

There are several immunohistochemical markers used in the evaluation of melanocytic lesions; S-100 remains the most sensitive marker for melanocytic lesions, but a handful of others, including MART-1/Melan-A, HMB-45, MITF, and tyrosinase have good specificity for malignancy. More recently, the melanoma-associated antigen PRAME (preferentially expressed antigen in melanoma) has been identified as both sensitive and specific for melanocytic tumors. In a study of 400 melanocytic tumors, diffuse nuclear immunoreactivity for PRAME was detected in 83% of primary melanomas and 87% of metastatic lesions. Of the 140 benign melanocytic nevi, 84% were completely negative for PRAME.[25–29] PRAME is emerging as a marker to distinguish malignant from benign melanocytic tumors.

Pitfalls

There are limitations with each of the melanoma-associated antigens used in immunohistochemistry to distinguish melanocytic tumors. Overestimation with Melan-A or underestimation with S100 of epidermal melanocytes can lead to overdiagnosis and underdiagnosis, respectively, of melanoma in situ.

Comparative Genomic Hybridization

Basics

The principal type of cytogenetic assay currently in use is comparative genomic hybridization (CGH), initially introduced in 1992, and more recently applied to melanoma. The goal of the technique is to evaluate for either gains or losses of either whole chromosomes or regions of chromosomes.[20,21] Total genomic DNA is isolated from both normal tissue and the tumor and labeled with various fluorochromes. The mixture is

Table 2
Molecular studies for diagnosis of atypical melanocytic proliferations

	Utility in Diagnoses	Advantage	Limitations
IHC	MIS; solar lentigines; and AIMP	Useful with limited tissue	Overestimation (with Melan-A) or underestimation (with S100) of epidermal melanocytes can lead to over- and underdiagnosis, respectively, of MIS
CGH	Benign melanocytic nevi and malignant melanoma	Evaluates full set of chromosomes	Not useful with limited and heterogeneous tissue
FISH	Melanoma, atypical melanocytic nevi, and ambiguous melanocytic proliferations	Optimal assay for limited amounts of tissue Sensitivity of 80%–100% and specificity of 95% for diagnosing melanoma	Targets only specific chromosomal aberrations False-positive tests secondary to polyploidy
Gene expression signature and mutational analyses	Benign melanocytic nevi and malignant melanoma	Classifies melanocytic lesions as benign or malignant with a sensitivity of 90% and a specificity of 91%	Further validation needed, especially in large cohorts of difficult atypical melanocytic proliferations and melanoma subtypes

Abbreviations: AIMP, atypical intraepidermal melanocytic proliferation; CGH, comparative genomic hybridization; FISH, fluorescent in situ hybridization; H&E, hematoxylin and eosin; IHC, immunohistochemistry; Melan-A, melanoma antigen recognized by T cells 1; MIS, melanoma in situ.

hybridized with metaphase chromosomes from a healthy donor (classic CGH) or genomic DNA (array CGH). Copy-number gains or losses are detected based on differences in fluorescence intensity.

Clinical applications

CGH is the most widely used diagnostic tool for the work-up of histologically ambiguous melanocytic proliferations. The most common chromosomal aberrations that distinguish melanocytic nevi from melanoma are gains in chromosome 7 with loss of 9q and 10.[30–32] The approach has an estimated sensitivity and specificity of 80% and 90%, respectively, but false-negative results may arise because of the failure to detect chromosomal aberrations in small populations of tumor cells (Fig. 1).

Pitfalls

Detection of an isolated copy-number change must be interpreted with caution. A Spitz nevus or tumor, for example, that show a loss of chromosome 3 or a gain in 11p, but otherwise lack worrisome features on morphologic analysis, are likely an indolent lesion. Heterogeneity in the tumor can also be a problem for interpretation

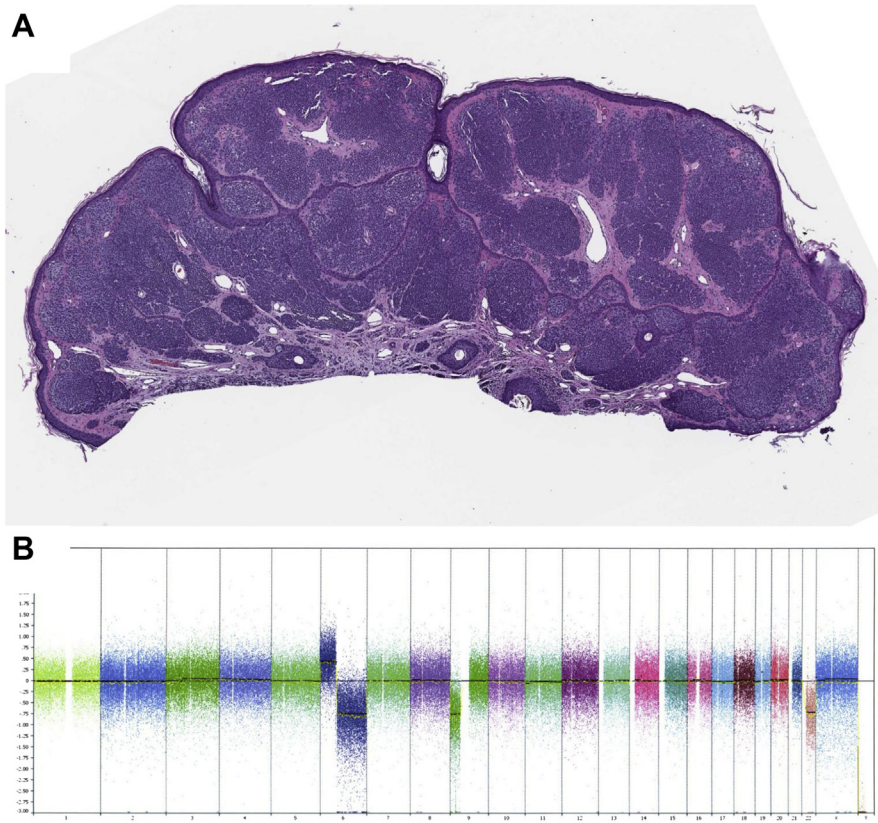

Fig. 1. Nevoid melanoma from the cheek of a young woman. (*A*) The microscopic findings of the lesion suggest a possible congenital nevus, but also showed features worrisome for melanoma. (*B*) SNP array analysis of the tumor revealed multiple unbalanced genomic aberrations, including gain of 6p, loss of 6q, and loss of 9p, including homozygous deletion of the CDKN2A gene, and loss of 22q.

of CGH. In general, roughly one-third of the tumor has to have copy-number changes to be detected by CGH.[33]

Fluorescence In Situ Hybridization

Basics

Fluorescence in situ hybridization (FISH) is an assay that evaluates individual chromosomes or particular regions within a chromosome. The basic technique involves binding of a fluorescently labeled oligonucleotide probe, specific for its complementary DNA sequence, and visualization with fluorescence microscopy. There are 2 general types of FISH probes—centromeric probes and allele-specific probes—relevant for the diagnostic work-up of atypical melanocytic lesions[33]. Centromeric probes bind to a centromeric region of a specific chromosome, thereby determining the number of copies of that chromosome. Allele-specific probes bind to a specific sequence of DNA to evaluate for aberrations that may be relevant to melanocytic lesions. One advantage of FISH is the ability to detect subpopulations of cells within a heterogeneous biopsy sample (Fig. 2).

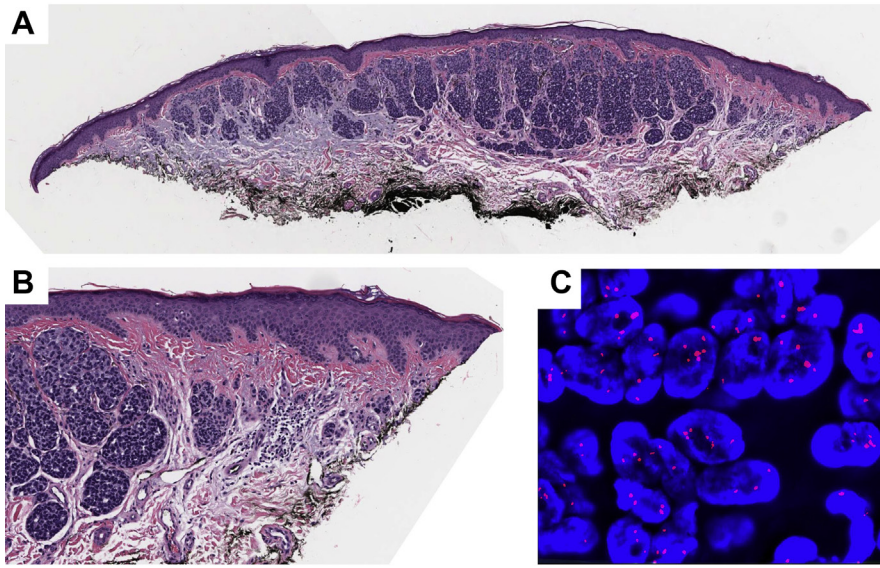

Fig. 2. Atypical melanocytic proliferation from the ear of an elderly man. (*A*) The pathologist who initially reviewed the findings was unsure as to whether the lesion was an atypical nevus or melanoma. (*B*) Juxtaposition of more densely cellular melanocytes with hyperchromatic nuclei and adjacent blander nevus-like melanocytes at the edge of the biopsy. (*C*) FISH analysis revealed gains of 6p25 in more than 90% of atypical melanocytes, but not in the bland nevus cells. More than half of the atypical melanocytes also showed gain of 11q13 (not shown). A diagnosis of melanoma associated with a nevus was rendered.

Clinical applications

Compared with CGH, FISH can be more reliably used on biopsy specimens with limited tissue. It is also cheaper and more widely available because it requires less technical expertise. The 4-probe FISH assay—targeting genes on 6p25, 6q23, 11q13, and centromere 6—is used to differentiate between melanoma and benign nevi. The initial assay used to describe this approach had 87% sensitivity and 95% specificity for melanoma.[33] For diagnostically ambiguous melanocytic proliferations, the use of FISH is mixed. In 1 study, Gerami and colleagues[34] examined 27 ambiguous lesions with FISH; all FISH-positive lesions ultimately metastasized.[16] Another study showed a specificity of 50% and a sensitivity of 60% for metastases.[23,35]

Pitfalls

There are several limitations to FISH. First, it only evaluates for genetic aberrations in the targeted areas, which is typically limited to 4 chromosomal loci. This is in contrast to CGH, which evaluates the complete set of chromosomes. Second, a negative FISH does not exclude malignancy. There are bona fide cases of melanoma diagnosed unequivocally by morphologic studies that do not have copy-number changes on FISH. The specificity of FISH for melanoma is also not perfect. The most common scenario in which one sees false-positive FISH results arise is when benign lesions exhibit polyploidy. It has been shown that a minority of Spitz nevi, for example, is tetraploid in which there are 4 copies per nucleus of any chromosome tested. In this case, this is not a limitation of FISH per se, but rather the recognition that a gain in chromosomal copy number can be seen in unequivocally benign lesions.

Mutational Analyses and Gene Expression Signatures

Basics

A better understanding of melanoma genomics has enabled the use of mutational analyses as diagnostic adjuncts. Several genomic and somatic mutations in genes have been identified in melanoma, including PTEN, GNAQ/GNA11, KIT, MAP2K1/2, BRAF, and NRAS; many of these can also be detected in melanocytic nevi.[33]

Clinical applications

Mutational analyses show promise in discriminating melanoma from benign counterparts. In a study of 437 specimens, a 23-gene probe demonstrated a sensitivity of 90% and specificity of 91% in differentiating benign nevi from melanoma.[36] When this technique was compared with CGH, the results were largely similar in distinguishing melanoma and benign lesions, but showed discordant results for histologically ambiguous melanocytic proliferations.[37]

Pitfalls

Molecular studies have a lot of potential to help in the diagnosis of atypical melanocytic lesions for which conventional histologic techniques have reached their limits. Although all of these approaches require additional validation studies and long-term follow-up, each have utility, especially when ambiguity of diagnosis leaves us without one.

NATURAL HISTORY

The natural history of atypical cutaneous lesions, particularly the issue of whether they may progress to invasive malignancy, is poorly understood. There are a handful of observational studies that provide some insight. Here we will highlight studies of patients with a diagnosis of AIMP, DNIEMD, AJMH, MELTUMP, or dermal BMT on initial biopsy that was changed to melanoma or melanoma in situ after complete excision of the lesion. This does not necessarily provide a full understanding of the natural history of a lesion, but gives a sense of either the risk of misdiagnosing melanoma or the risk that a lesion may progress to melanoma after excision.

Regarding AIMPs, in an analysis of 306 patients with an initial diagnosis of AIMPs on biopsy, the final pathology of the surgically excised specimen changed to melanoma in 4.2% of patients (13/306).[11] Among these melanomas, most were melanoma in situ (11/13 patients, 85%), but 2 patients had invasive melanoma (2/13 patients, 15%). Risk factors associated with a change in diagnosis to melanoma included extension of the AIMP to the base of the biopsy specimen and location of the tumor on head, neck, and acral areas.

In a retrospective analysis of 82 skin biopsies initially diagnosed as DNIEMD, 8 lesions (9.8%) were melanoma.[38] This was consistent with a larger study of 263 patients with DNIEMD that described an increased association with dysplastic nevi and melanoma[39], suggesting that DMIEMD may be a precursor lesion or marker of increased risk of melanoma.

The likelihood of upstaging to melanoma from an initial diagnosis of AJMH was reported to be zero in a small retrospective study of 27 patients treated at a private dermatology practice.[40] Of the 27 patients, none were found to have melanoma on final surgical specimen. In addition, analysis of 19 patients (19/27, 70%) who had follow-up ranging from 2 to 6 years did not have recurrence of AJMH.

The risk of metastatic spread is thought to be higher for lesions that involve the dermis, such as MELTUMP and BMT. A prospective study of 32 patients with BMT who underwent both wide local excision and sentinel lymph node biopsy showed that the dermal variant of this lesion demonstrates regional lymph node involvement.[15]

Retrospective studies of MELTUMP showed lymphatic invasion in 25% of patients and this was associated with melanoma metastases and melanoma-specific death.[8] A retrospective review of MELTUMP tumors estimates the risk of developing regional metastases or disease-specific death from 1% to 2.4%.[41,42] Having noted this, it is important to emphasize that the natural history of lymph node involvement associated with MELTUMPS is far from clear. Regional lymph node involvement is not synonymous with malignancy; there are reports of bona fide benign nevi that spread to cutaneous lymphatics or lymph nodes.[23] Indeed, many MELTUMPs with involvement of lymph nodes demonstrated an indolent course.

Management

Although there are no evidence-based guidelines on treatment of atypical melanocytic proliferations, the general consensus is to stratify risk based on the layer of skin involved. For lesions confined to the epidermis on biopsy, surgical treatment is re-excision of biopsy site with negative margins. For atypical lesions involving the dermis, treatment involves wide local excision (ie, the same as melanoma) because of the afore-mentioned risk of distant metastases. Among the lesions with the dermal component, the most commonly reported are dermal BMT and MELTUMP.

A general principle of treatment of ambiguous cutaneous pigmented lesions is that the therapy should be adequate for the highest-risk entity in the differential diagnosis. If melanoma in situ or invasive melanoma is among the differential diagnosis, it ought to be treated as such. A second treatment principle is that clinicians must to be transparent in discussing the ambiguity of the pathology report and the difficulty of assessing the risk of frank malignancy. A discussion of whether to monitor, rebiopsy, or excise depends on factors that are not exclusively found in the pathology report. Adequacy of margins, for example, may differ based on anatomic location and the cosmetic results. A child with a completely excised conventional Spitz nevus on the eyelid, for example, may not warrant re-excision that results in a disfiguring scar, particularly if there is no diagnostic uncertainty or atypia.

There are alternative treatments for atypical melanocytic proliferations. Mohs micrographic surgery or staged excision can be considered for cosmetically challenging areas where adequate margins are difficult to obtain without disfiguring results. In patients who are poor surgical candidates, or with lesions such as lentigo maligna on the face that have expansive indeterminate boundaries, topical 5% imiquimod cream has been studied as an adjuvant treatment. One retrospective cohort study found that 94% of patients had clearance of lentigo maligna after treatment with surgery and imiquimod, with a mean follow-up of 43 months.[43]

SUMMARY

Here, we have highlighted the challenge of interpreting a pathology report that includes one of the many variants of ambiguous pigmented skin lesions. There are no consensus guidelines on treatment because fundamental questions about the nomenclature, classification, diagnostic criteria, and natural history of these lesions is poorly understood. Despite this poor understanding, surgeons must make real decisions in the clinic about whether to treat patients, knowing that the benefit of excising an atypical melanocytic lesion is unclear in many cases and potentially disfiguring. The reality of uncertainty demands that surgeons have as extensive an understanding as possible to help communicate to their patients the ambiguous nature of an atypical melanocytic lesion and its treatment.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Kim JC, Murphy GF. Dysplastic melanocytic nevi and prognostically indeterminate nevomelanomatoid proliferations. Clin Lab Med 2000;20:691–712.
2. Briggs JC. Melanoma precursor lesions and borderline melanomas. Histopathology 1985;9:1251–62.
3. Cheung WL, Smoller BR. Dermatopathology updates on melanocytic lesions. Dermatol Clin 2012;30:617–22.
4. Mills OL, Marzban S, Zager JS, et al. Sentinel node biopsy in atypical melanocytic neoplasms in childhood: a single institution experience in 24 patients. J Cutan Pathol 2012;39:331–6.
5. Wick MR, Patterson JW. Cutaneous melanocytic lesions: selected problem areas. Am J Clin Pathol 2005;124(Suppl):S52–83.
6. Rywlin AM. Intraepithelial melanocytic neoplasia (IMN) versus intraepithelial atypical melanocytic proliferation (IAMP). Am J Dermatopathol 1988;10:92–3.
7. Pie rard GE, Pie rard-Franchimont C, Delvenne P. Simulants of malignant melanoma. Oncol Rev 2015;9:278.
8. Abraham RM, Karakousis G, Acs G, et al. Lymphatic invasion predicts aggressive behavior in melanocytic tumors of uncertain malignant potential (MELTUMP). Am J Surg Pathol 2013;37:669–75.
9. Zhang J, Miller CJ, Sobanko JF, et al. Frequency of and factors associated with positive or equivocal margins in conventional excision of atypical intraepidermal melanocytic proliferations (AIMP): a single academic institution cross-sectional study. J Am Acad Dermatol 2016;75:688–95.
10. Lott JP, Elmore JG, Zhao GA, et al. Evaluation of the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) classification scheme for diagnosis of cutaneous melanocytic neoplasms: results from the international melanoma pathology study group. J Am Acad Dermatol 2016;75:356–63.
11. Zhang J, Miller CJ, Sobanko JF, et al. Diagnostic change from atypical intraepidermal melanocytic proliferation to melanoma after conventional excision—a single academic institution cross- sectional study. Dermatol Surg 2016;42:1147–54.
12. Chisholm C, Greene JF. Progression from atypical/dysplastic intraepidermal proliferations and carcinoma in situ to invasive tumors: a pathway based on current knowledge. Am J Dermatopathol 2011;33:803–10.
13. Urso C, Giannini A, Bartolini M, et al. Histological analysis of intraepidermal proliferations of atypical melanocytes. Am J Dermatopathol 1990;12:150–5.
14. Rywlin AM. Malignant melanoma in situ, precancerous melanosis, or atypical intraepidermal melanocytic proliferation. Am J Dermatopathol 1984;6(Suppl):97–9.
15. Magro CM, Crowson AN, Mihm MC, et al. The dermal-based borderline melanocytic tumor: a categorical approach. J Am Acad Dermatol 2010;62:469–79.
16. Magro CM, Abraham RM, Guo R, et al. Deep penetrating nevus-like borderline tumors: a unique subset of ambiguous melanocytic tumors with malignant potential and normal cytogenetics. Eur J Dermatol 2014;24:594–602.
17. Zembowicz A, Scolyer RA. Nevus/melanocytoma/melanoma: an emerging paradigm for classification of melanocytic neoplasms? Arch Pathol Lab Med 2011;135:300–6.
18. Scolyer RA, Murali R, McCarthy SW, et al. Histologically ambiguous ("borderline") primary cutaneous melanocytic tumors: approaches to patient management

including the roles of molecular testing and sentinel lymph node biopsy. Arch Pathol Lab Med 2010;134:1770–7.
19. Margo CE, Roper DL, Hidayat AA. Borderline melanocytic tumor of the conjunctiva: diagnostic and therapeutic considerations. J Pediatr Ophthalmol Strabismus 1991;28:268–70.
20. Weedon D. Borderline melanocytic tumors. J Cutan Pathol 1985;12:266–70.
21. Brodell RT, Santa Cruz DJ. Borderline and atypical melanocytic lesions. Semin Diagn Pathol 1985;2:63–86.
22. Elder DE, Xu X. The approach to the patient with a difficult melanocytic lesion. Pathology 2004;36:428–34.
23. Mooi WJ. "Lentiginous melanoma": full-fledged melanoma or melanoma precursor? Adv Anat Pathol 2014;21:181–7.
24. Zembowicz A. A new perspective for the classification of melanocytic lesions. In: 4th Melanoma Pathology Symposium of the International Dermatologic Surgery Melanoma Pathology Working Group. Tampa, FL: John Wiley & Sons; 2011; p. 1012.
25. Pusiol T, Piscioli F, Speziali L, Zorzi MG, et al. Clinical features, dermoscopic patterns, and histological diagnostic model for melanocytic tumors of uncertain malignant potential (MELTUMP). Acta Dermatovenerol Croat 2015;23:185–94.
26. Pusiol T, Morichetti D, Piscioli F, Zorzi MG. Theory and practical application of superficial atypical melanocytic proliferations of uncertain significance (SAMPUS) and melanocytic tumours of uncertain malignant potential (MELTUMP) terminology: experience with second opinion consultation. Pathologica 2012;104:70–7.
27. Mö ller MG, Pappas-Politis E, Zager JS, et al. Surgical management of melanomain- situ using a staged marginal and central excision technique. Ann Surg Oncol 2009;16:1526–36.
28. Hazan C, Dusza SW, Delgado R, et al. Staged excision for lentigo maligna and lentigo maligna melanoma: a retrospective analysis of 117 cases. J Am Acad Dermatol 2008;58:142–8.
29. Lezcano C, Jungbluth AA, Nehal KS, et al. PRAME expression in melanocytic tumors. Am J Surg Pathol 2018;42(11):1455–65.
30. Bastian BC, LeBoit PE, Hamm H, et al. Chromosomal gains and losses in primary cutaneous melanomas detected by comparative genomic hybridization. Cancer Res 1998;58:2170–5.
31. Bastian BC, Kashani-Sabet M, Hamm H, et al. Gene amplifications characterize acral melanoma and permit the detection of occult tumor cells in the surrounding skin. Cancer Res 2000;60:1968–73.
32. Bastian BC, Olshen AB, LeBoit PE, et al. Classifying melanocytic tumors based on DNA copy number changes. Am J Pathol 2003;163:1765–70.
33. Ensslin CJ, Hibler BP, Lee EH, et al. Atypical melanocytic proliferations: a review of the literature. Dermatol Surg 2018;44:159–74.
34. Gerami P, Jewell SS, Morrison LE, et al. Fluorescence in situ hybridization (FISH) as an ancillary diagnostic tool in the diagnosis of melanoma. Am J Surg Pathol 2009;33:1146–56.
35. Warner TF, Seo IS, Bennett JE. Minimal deviation melanoma with epidermotropic metastases arising in a congenital nevus. Am J Surg Pathol 1980;4:175–83.
36. Clarke LE, Warf MB, Flake DD, et al. Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. J Cutan Pathol 2015;42:244–52.
37. Wang G, Wang M, Alomari A, et al. Comparison of genomic abnormalities and gene expression analysis in atypical, ambiguous and malignant melanocytic

lesions. In: United States and Canadian Academy of Pathology Annual Meeting. Seattle, WA. 2016; p. 137A.
38. Sachdeva M, Frambach GE, Crowson AN, et al. De novo intraepidermal epithelioid melanocytic dysplasia as a marker of the atypical mole phenotype—a clinical and pathological study of 75 patients. J Cutan Pathol 2005;32:622–8.
39. Jessup CJ, Cohen LM. De novo intraepidermal epithelioid melanocytic dysplasia: a review of 263 cases. J Cutan Pathol 2010;37:852–9.
40. El Tal AK, Mehregan D, Malick F, et al. Atypical junctional melanocytic hyperplasia: a study of its prognostic significance. J Am Acad Dermatol 2012;66:AB141.
41. Kaltoft B, Hainau B, Lock-Andersen J. Melanocytic tumour with unknown malignant potential—a Danish study of 67 patients. Melanoma Res 2015;25:64–7.
42. Green RJ, Taghizadeh R, Lewis CJ, et al. Melanocytic tumours of uncertain malignant potential (MELTUMPs)—a diagnostic and management dilemma. Eur J Plast Surg 2015;38:13–6.
43. Swetter SM, Chen FW, Kim DD, et al. Imiquimod 5% cream as primary or adjuvant therapy for melanoma in situ, lentigo maligna type. J Am Acad Dermatol 2015;72:1047–53.