Melanocytic lesions on Genital Skin
Melanoma vs. Melanocytic Nevus, Revisited

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I. IS IT BENIGN OR IS IT MALIGNANT?

One of the commonest determinations we make as dermatopathologists is the determination of benignancy or malignancy of melanocytic neoplasms. While we make such judgments as to be routine and most are undoubtedly reasonably accurate, obviously an incorrect judgment in this regard can have profound implications for both the patient and the physician. An incorrect judgment either leaves the patient at risk for undertreatment or overtreatment of their disease, and an errant diagnosis also leaves the physician culpable in the medicolegal arena. Although most dermatopathologists see cases daily in which varying levels of uncertainty arise, we often cover our doubts with exact language that sometimes implies we know more than we actually do. We evaluate a case and we debate about whether it is a melanocytic nevus or a melanoma, and then we issue a diagnosis: benign or malignant. We do this because we live in an era in which patients and their families increasingly believe that an exact diagnosis should always be possible. There is considerable pressure on us as pathologists and dermatopathologists to make an exact judgment of benignancy or malignancy, even in instances when are diagnostic surety is less than absolute.

In this session, we will review benign and malignant proliferations with a special emphasis on melanocytic lesions involving genital skin and flexural skin.

Over time, we as pathologists need to pursue new approaches to diagnosis that will yield additional information of importance to patients, even as these approaches threaten to render our existing approach obsolete. Genomic analysis (comparative genomic hybridization or CGH) holds considerable hope as a tool in this setting. FISH analysis can also be utilized as a method to screen for melanoma-associated genomic anomalies.

II. WHOSE CRITERIA SHOULD I USE? WHICH CRITERIA SHOULD I USE? WHAT SHOULD I DO WHEN CRITERIA CONFLICT?

Even as we sit at the inception of the 21st century, there are no clear answers to these rhetorical questions.

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Although many criteria for melanoma diagnosis have been forwarded, the reliability (sensitivity and specificity) of any given criterion remains unknown in any precise way, even after years of use. Furthermore, even if all pathologists and dermatopathologists used identical criteria, which is clearly not the case, the histopathologic diagnosis of melanoma remains subjective as the weight attributed to any given criterion varies greatly among observers. Although it is clear that strides have been made, the microscopic diagnosis of melanoma remains as much an art as a science. The diagnosis depends not only upon which criteria are utilized but also upon how the criteria are applied and interpreted, the weight given to each individual criterion, and the summary assessment when inevitable conflicts in criteria arise.

Evan Farmer’s analysis of “expert” diagnosis from 1996 is troubling, as it implies that there is wide variability amongst our best experts with respect to the exact diagnosis of a wide spectrum of melanocytic neoplasms. If our experts are not making reproducible diagnoses, it seems likely that even greater variability exists in the general realm. In a prototypical pattern of melanoma, with an asymmetrical proliferation of strikingly atypical melanocytes arrayed confluenty within the epidermis and as sheets in the dermis, the concordance rates among different observers should be very high. Unhappily, this may not be the case.

It is often said that “more” or “better” criteria are needed for the diagnosis of melanoma and melanocytic neoplasms. Rather than inventing evermore criteria, perhaps greater impact would be achieved with more objective application and interpretation of existing criteria, supplemented by algorithms to be utilized when criteria are found to conflict. What do we mean by “pagetoid” scatter? How much scatter is required for diagnostic meaning? What is confluence? What is atypia? How much variability in size and shape of nests is permitted? Until we can answer questions such as these, we cannot hope to utilize conventional microscopy to its best effect. Our collective goal must be to stride toward greater diagnostic reproducibility. While a reproducible diagnosis is not necessarily a correct diagnosis, reproducibility clearly holds major importance in the study of biological behavior and outcome.

Increasingly, FISH and CGH analysis can also be integrated into the evaluation of melanocytic lesions as diagnostic tools. If genomic aberrations are detected by either testing method, it tends to favor classification as melanoma. Current FISH analysis has limited diagnostic efficacy because the probe sets that have been developed for analysis to date tend to be restricted in scope. Our current FISH analysis screens for anomalies involving chromosomes 6 and 11 (including the CCND1 gene) exclusively.

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III. IS IT MELANOCYTIC DYSPLASIA OR A NESTED PATTERN OF MELANOMA?

This issue is closely related to limitations of existing criteria discussed above.

In the eyes of many, “pagetoid spread” is the stereotypical pattern of melanoma in situ and melanoma. In my opinion, an over-reliance on pagetoid scatter as a diagnostic criterion may be a hindrance to the recognition of many melanomas that display a predominantly nested pattern. This is especially true of melanomas that develop on severely sun-damaged skin, including the pattern of melanoma that falls under the rubric of lentigo maligna or lentigo maligna melanoma. If the interpreting pathologist requires florid pagetoid scatter before a diagnosis of melanoma can be forwarded, melanomas with a predominance of nests are problematic to classify and are often signed out descriptively. This feeds the use of euphemistic terms such as “atypical melanocytic hyperplasia” or “atypical melanocytic proliferation” or “severe dysplasia,” even in the face of architectural aberrations that overwhelmingly point to melanoma as the best diagnosis.

IV. WHAT ARE THE VARIOUS CONSIDERATIONS IN MY DIFFERENTIAL DIAGNOSIS?

The lentigo family: with respect to genital skin, the chief considerations include lentigo simplex and melanotic macules. Lentigo simplex represents a proliferation, typically of small breadth, of small single melanocytes along the junctional zone. Because of a predominance of single cells, over-interpretation as melanoma in situ represents a pitfall. Melanotic macules represent pigmented lesions that may have a slight increase in melanocytes within them, but the process is generally considered to be non-melanocytic in nature. Some melanotic macules have highly varied pigmentation and can be multifocal. In the extreme case, the clinical resemblance to melanoma in situ can be striking.

Lentiginous melanocytic nevi: these are benign melanocytic proliferations with both single cells and nests at the junction. Small melanocytes may be positioned in the dermis below this as well.

Dysplastic melanocytic nevi: many melanocytic nevi on genital skin, flexural skin, or skin of the breast have stromal alterations associated with them. Whether these lesions should be termed “dysplastic” or “nevi of special sites” represents an issue of style that can vary considerably amongst...
different consultants. My opinion and philosophy is that the usage of the
term “dysplastic” should be minimized in this context.

Melanocytic nevi of special sites: as noted above, these lesions may occur
on genital, breast, or flexural skin. Attributes such as epithelioid melanocyte
morphology, fine dusty melanization, bridging, and lamellar fibroplasia are
commonplace. As noted above, there is extreme overlap with the spectrum
of what can be called “dysplastic,” and considerable variation can be seen
amongst various experts in this regard.

Inflamed melanocytic nevi: especially on genital skin, juxtaposed
inflammation can create a risk for an overcall of melanoma. A melanocytic
nevus with superimposed lichen sclerosis represents a key pitfall to avoid.

Melanoma in situ and invasive melanoma: malignancies of melanocytes
clearly occur on the sun-protected skin of the genital and perigenital region.
While criteria such as size, symmetry, circumscription, pattern of nesting,
and confluence remain key diagnostic tools, it remains a challenging area of
diagnosis because many genital melanocytic nevi show attributes that
overlap with melanoma. In particular, large nests of melanocytes, epithelioid
melanocytes, and confluence can all be seen in genital melanocytic nevi
and should not be relied on as conclusive evidence of melanoma,
particularly in a younger patient.

V. ANCILLARY TOOLS

In general, immunoperoxidase staining will not enable a decisive diagnosis
of “benign vs. malignant” to be made. Lineage-specific stains such as
Melan-A, SOX-10, and MiTF are of value to demonstrate the distribution of
melanocytes, particularly if it is ambiguous because of juxtaposed
inflammation. Ki-67 staining can be of value when the cell proliferation rate
is substantially elevated, as concern for the possibility of melanoma is
raised. If Ki-67 labeling is low, caution should be exerted, as this can be
seen with benignancies but can also be encountered in melanomas with low
cellular turnover. In my view, HMB-45 has little value as an ancillary staining
tool.

FISH analysis can be of value in the assessment of atypical melanocytic
proliferations with a mostly nested configuration. The testing is not easily
applied to lesions with a predominance of single cells or to lesions of small
diameter. In these situations, it is difficult to identify the lesional cells of
interest in the dark-field environment where testing occurs.

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CGH analysis remains the best testing method to assess the entire genome of a melanocytic tumor. It is best applied to nodular lesions where significant DNA can be extracted for analysis. Using array testing methodology, we anticipate turnaround times of 3-4 weeks.

References


