

## The Role of Histopathology in Melanoma Diagnosis and Prognosis.

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### Introduction:

Cancers including melanomas can be defined in terms of two major potential harmful but not necessarily lethal properties, namely the potential for local persistence and recurrence, and the potential for systemic metastasis (1). The essential purpose of histopathologic evaluation of clinically problematic melanocytic lesions is to accurately rule out malignancy, distinguishing melanomas from their important simulants. These include a panoply of benign lesions that are described in textbooks and reviews of dermatology and pathology (2-4). Among these, the major potential simulants are benign nevi including congenital nevi, common acquired nevi, and special forms of nevi such as dysplastic nevi and nevi of special sites. Spitz nevi may be especially problematical as simulants, and appear to involve different genetic pathways from the other acquired nevi (5). Blue nevi and related lesions which include cellular blue nevi and deep penetrating nevi, epithelioid blue nevi, and pigmented epithelioid melanocytomas complete the list. Most of these lesions have no significance except as simulants of melanoma. Nevi in general, and especially dysplastic nevi, also have significance as markers of individuals at increased risk for the development of melanoma, and this is true for both clinically and histologically diagnosed dysplastic nevi (6-9). Thus, a secondary role of histopathology is the determination of atypia in dysplastic nevi, because this has been correlated with melanoma risk. In addition, histopathology plays an important role in the assessment of prognosis for individuals with a diagnosis of melanoma. This latter topic will be the major theme of this brief monograph.

### Tumor progression and metastasis.

As noted above, cancers may cause problems in terms of local recurrence, or distant metastasis, or both. Melanomas, like most cancers, evolve through a stepwise process of "tumor progression" and may be diagnosed in early or later stages of progression. (1;10;11). The phenomena of tumor progression were characterized in the latter part of the last century prior to knowledge of the genetic underpinnings of cancer. Today, most of the events of tumor progression are considered to be the result of sequential acquisition of genetic abnormalities (12), modulated by host factors in the microenvironment and systemically, including the stroma, the lymphocytes, and the vasculature. Melanomas that are diagnosed in the early stage of tumor progression present clinically as patches or plaques which spread along the radii of an imperfect circle in the skin, and have thus been termed "radial growth phase" melanomas (13-15). Histologically, the radial growth phase is defined as a lesion in which neoplastic cytologically atypical melanocytes are present in the epidermis and may be present in the dermis as well (16). When confined to the epidermis, the lesion is termed "melanoma in situ". In an interesting and poorly

understood phenomenon that also occurs in benign nevi, lesional cells from an in situ melanoma may migrate from the epidermis into the dermis. Since the same process occurs in benign nevi and in malignant melanomas, this process probably does not constitute "invasion" in the usually understood sense of the word.

In the initial stages of this migration, the melanoma cells lack the capacity for proliferation in the dermis in that they are not mitotically active and they do not form "tumors" -- in the true sense of the word where the term is indicative of a mass lesion caused by proliferation of cells. These "non-tumorigenic" and "nonmitogenic" invasive melanomas typically have capacity for local persistence and regrowth if not completely excised, and they also have the capacity for progression to the next stage of "tumorigenic melanoma". However, they do not have capacity for metastasis. This latter may seem paradoxical since the lesions are considered to be "cancers". However, it is reasonable to consider a lesion to be a cancer if it has capacity for persistence, regrowth, and progression to a more fully malignant neoplasm, even in the absence of capacity for metastasis. It is also not surprising that a cancerous lesion which is nontumorigenic at the primary site might not have capacity for metastasis since a metastasis, or at least a clinically significant metastasis, is a lesion in which the cells have the capacity for tumorigenic proliferation at distant sites.

In the tumorigenic phase of melanoma progression, the lesional cells have acquired capacity for proliferation in the dermis which occurs "vertically", or perpendicular to the direction of the epidermis, and has therefore been termed the "vertical growth phase" (13-15). In a histological section, the vertical growth phase may appear circular and the radial growth phase may appear linear and has therefore been termed to the "horizontal growth phase" by some. Tumorigenic melanomas may evolve in one of two ways. First, a tumor may be formed by the "accretive" growth of multiple nests of cells piling up on one another much as a brick wall is built, in a process originally described by Reed as "variant vertical growth" (17), and by Tuthill (18) as the "dysplasia-melanoma sequence". Again, this process probably resembles the evolution of compound nevi from junctional nevi rather than a process of true "invasion". In such a situation, the capacity for proliferation in the dermis is not necessary, and the prognosis for these "accretive" but "non-tumorigenic" and "nonmitogenic" vertical growth phase melanomas is very good with a very low probability of metastasis (19). In the second, "expansile" pattern of vertical growth phase, which is much more common and also more significant prognostically, one or more of the small clusters of cells present in a radial growth phase melanoma appears to acquire the capacity to expand in space and time much as a balloon expands as it is blown up (10;11). In this manner, a true tumor is formed, visualized as a swelling or lump, sometimes thought by patients to be a "blister", appearing in the background of the radial growth phase lesion. In some cases, termed "nodular melanomas", the tumorigenic stage appears in the absence of a pre-existing radial growth phase, and such lesions, termed "nodular melanomas" are difficult to diagnose both clinically and histologically (20-22). Expansile growth in any tumorigenic melanoma appears to occur by a process of cell division, and mitotic activity is typically although not invariably observed histologically (19). In a few very early lesions that have acquired the capacity for proliferation in the dermis, the tumor is not yet formed but mitotic

activity is observed in the dermis. These lesions may be termed "mitogenic" but "non-tumorigenic" vertical growth phase melanomas. There is abundant evidence that mitogenicity, like tumorigenicity, is associated with increased competence for metastasis even in a thin melanoma (19;23-32).

#### Metastasis and micrometastasis.

Systemic metastasis typically presents some time (often measured in years) after definitive treatment of a tumorigenic and/or mitogenic melanoma, and is not usually accompanied by persistence or regrowth of tumor at the primary site. Therefore, micrometastases as "seeds" of the later to be evident metastases must have been present in distant organs at the time the primary was removed. Micrometastases, by definition, are not observable clinically, and are therefore diagnosed histologically. With increasing sensitivity of diagnostic tools, this situation may change in the future. Most micrometastases that are presently observed histologically are detected in sentinel lymphadenectomy specimens. In this procedure, the "sentinel", or gatekeeper node is removed and studied with immunohistochemical techniques as well as routine light microscopy (33). Immunohistochemistry is used to highlight the lesional cells, much as a hunter's yellow jacket makes him conspicuous in a green forest. Micrometastases can be found by these means, even sometimes at the single and a cell level, or more typically as small clusters of cells. These micrometastases appear to be "dormant", without detectable proliferative or angiogenic activity, while clinically evident macrometastases do express these attributes (34;35). The role of dormancy of micrometastases, which presumably occur in brain, lungs, liver and other distant organs as well as in sentinel nodes, should be a focus of intensive study, although this is difficult to accomplish because of the elusive nature of these lesions. If dormancy could be maintained in a patient's micrometastases, clinical metastases would not occur, and the patient's survival would be indefinitely prolonged. Better, of course, is to prevent the development of micrometastases by diagnosing melanomas in an early stage (36), such as the radial growth phase, when the probability of the existence of micrometastases approaches zero (10;37).

#### Microstaging systems for melanoma

As already mentioned, an important role of histopathology, in addition to establishing an accurate diagnosis, is in the prediction of survival probability. In the present inadequate state of therapeutic intervention, this is tantamount to the probability of development of clinical metastasis, which in turn is equivalent to the probability of micrometastases being present at the time of diagnosis. Microscopically determined attributes that have been associated with metastasis, in addition to the newer concepts of tumorigenicity and mitogenicity, include Clark's level of invasion (13;14), Breslow's thickness measurement (38;39), ulceration (40), mitotic rate (31;32;41), tumor-infiltrating lymphocytes or TILs (31;42;43), angiolymphatic invasion (44;45), and others. Breslow thickness, ulceration, and Clark's level IV invasion are the attributes in use in the current AJCC staging system (46;47). Using these attributes in combinations, melanoma patients can be separated into

groups that are at low risk, or at intermediate or high risk for metastasis. This form of "microstaging" is used in routine clinical decision-making today.

Therapeutic decisions in a patient with melanoma revolve around the prevention of local recurrence, and the prevention of the development of systemic metastasis. For example, the prognosis in AJCC stage Ia "thin" (Breslow thickness < 1mm) melanomas is considered to be good enough that wide local excision to prevent local recurrence is sufficient, and sentinel lymph node sampling or adjuvant therapy, measures which are directed at regional or systemic metastases, are not considered to be indicated. AJCC stage Ib melanomas are those "thin" melanomas that have either Clark level IV invasion or ulceration. In these circumstances, the potential for regional metastasis is considered to be high enough that sentinel lymph node sampling is typically offered (48).

Recent studies from the Penn Pigmented Lesion Clinic by Gimotty et al. have highlighted the role of tumorigenicity and mitogenicity in further breaking down the "thin" melanoma groups into minimal, intermediate, and higher risk categories. In the AJCC database, the 10-year probability of metastasis was approximately 10%, although this number is considerably smaller in the population-based SEER database (49). Using tumorigenicity and mitogenicity as additional attributes, Gimotty et al. have demonstrated that patients with non-tumorigenic and nonmitogenic melanomas have a metastasis probability at 10 years approaching zero (i.e., 0.5%) (19;30;49). The rare metastasis that we have observed to occur in this group has been in patients whose tumors had extensive regression, suggesting that the melanoma may have been thicker (and had already metastasized) before the regression occurred. In an intermediate group, patients with tumorigenic but nonmitogenic melanomas have a low but definite probability (4.1%) of metastasis. Conversely, patients whose melanomas are tumorigenic and mitogenic have a probability of metastasis of as high as 12.5% in women and 31.7% in men. These findings have been validated in a "hold back" sample from the original data set. Findings from other institutions have tended to confirm the importance of tumorigenicity and mitogenicity (i.e. VGP) as melanoma risk factors, especially in thin melanomas (19;24;25;27;29;50-63). The importance of proliferation was also demonstrated in a recent study in which the proliferation marker Ki-67 was studied in a group of thin melanomas (19). Two high-risk groups were identified: men and women with dermal mitotic rate (MR) greater than 0 and dermal Ki67 expression  $\geq$  20% in tumor cells and men with MR greater than 0 and Ki67 expression less than 20%, with 10-year metastasis rates of 39% and 20%, respectively (19). It seems clear that this enhanced microstaging can contribute to routine management decisions today, and will be important for the stratification and optimal interpretation of clinical trials in the future.

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