Histopathology of Melanoma

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The accurate histopathological evaluation, the diagnosis, and the assessment of level of invasion of malignant melanoma have assumed a role of paramount importance in defining need for further surgery, a chemotherapeutic or immunotherapeutic approach to management, and prognosis. The classification of melanoma into lentigo maligna melanoma, superficial spreading melanoma, and nodular melanoma and further breakdown of those invasive melanomas into levels of invasion (Levels I–V) is the current practice and reflects the fact that the overall classification is clinocopathological rather than defined strictly by clinical or pathological criteria alone. Since any of the various types of melanoma may be invasive, the current terminology for determining invasion may be briefly reviewed. The definitions are set in anatomic terms so that there would seem to be little room for subjective variation in pathologic staging. By and large, this method has proven useful with a high percentage of unanimity of opinion among pathologists and dermatopathologists (1) (Fig. 1).

Level I. In Level I melanoma, all of the tumor cells are above the basement membrane. This, by definition, is in situ melanoma.

Level II. This anatomic level denotes involvement of the papillary dermis by malignant cells. The papillary dermis is composed of delicate collagen and ground substance and lies immediately deep to the basement membrane. It is most easily recognizable on low power scan of normal skin as that homogeneous eosinophilic area undulating in apposition to the rete pegs of the epidermis. An important additional consideration is that the papillary dermis surrounds skin appendages that may themselves plunge into the deeper portions of the skin. Hence, periappendageal tumor invasion may still be classified as Level II if the reticular dermis is not violated.

Level III. Here one sees invasion at the interface between papillary and reticular dermis. In this category there is some room for subjective variation in interpretation as this level is the least well defined anatomically. The reticular dermis is that portion of the dermis where the collagen is organized into readily distinguishable bundles. The interface between papillary and reticular dermis is Level III, although the anatomic demarcation may be indistinct due to a gradual transition from what is clearly papillary to what is clearly reticular dermis. There is additionally some variation in organization of the various layers of the dermis depending on the site of the sample. Other problems include distortion of the anatomy at this level due to scarring or inflammation together with the inevitable problem of deciding on a cell by cell basis which cells are benign, malignant, inflammatory, reactive fibroblasts, etc. Previous usage allowed Level III to be defined as widening and filling of the papillary dermis with impingement on the reticular dermis. It should be mentioned that the presence of single cells, strands of cells, or small nests of cells in the transition zone between papillary and reticular dermis or between collagen bundles of
FIG. 1. The five levels of invasion are defined by the arrows. This skin has mild sun damage. Level I: epidermis, Level II: the papillary dermis, Level III: the interface between papillary and reticular dermis, Level IV: reticular dermis, Level V: subcutaneous fat. H&E, 40×.

the upper reticular dermis does not justify assignment of the next highest level. Many Level III melanomas show a clear line of demarcation between the base of the tumor and the reticular dermis.

Level IV. Distinct invasion between collagen bundles of the reticular dermis is mandatory here.

Level V. All tumors that have invaded the subcutaneous tissues are classified as Level V.

The emphasis that the prognostic and therapeutic value from the examination of the biopsy or the excised lesion is a clinicopathological correlation cannot be
This lentigo maligna has increased numbers of atypical melanocytes in the basal layer (arrow). Cell morphology is highly variable from one cell to the other. The dermis contains melanophages and inflammatory cells, but there is no invasion. H&E, 250x.

overstated. Therefore, knowledge of the location on the skin of the lesion, growth history, and gross topography as correlated with the histology of the tumor is essential. A lentigo maligna melanoma may exhibit invasion to Level V. Nodular melanomas occasionally may be invasive only to Level II. Invading cells show no distinguishing characteristics as to the type of melanoma. The more superficial malignant cells in fact, particularly those in the epidermis, may provide the best clues as to the type of tumor.

PATHOLOGY OF CLINICAL CLASSIFICATION

Lentigo Maligna and Lentigo Maligna Melanoma

This lesion is characterized histologically by increased numbers of melanocytes and atypical melanocytes in the region of the basal layer of the epidermis (Fig. 2). There may be little or no separation of melanocytes by keratinocytes. Atypical features include enlarged nuclei, prominent nucleoli, and perhaps multinucleated cells; bizarre nuclear forms may be seen, but mitotic figures are uncommon. Single cells with enlarged nuclei, a moderately prominent nucleolus, and copious translucent cytoplasm present in the epidermis (pagetoid cells) are also rare in lentigo maligna melanoma. Melanocytic dendrites may be prominent in lentigo maligna melanoma. Invasion of cells into the papillary dermis is often associated with spindle cell alteration in the morphology of the cell, with nuclei becoming elongated and fibro-
blastlike. Pigmentation may be marked at sites of invasion. Histological invasion correlates well with the slightly raised or nodular dark areas seen grossly in lentigo maligna melanoma. The distinction between lentigo maligna and lentigo maligna melanoma is simply absence of dermal invasion in the former and presence of dermal invasion in the latter (Fig. 3). Otherwise, the histological features are similar so that accurate diagnosis is heavily dependent on accurate gross evaluation and sampling (2).

Superficial Spreading Melanoma

The histological hallmark of this lesion is the presence of pagetoid cells randomly scattered through all layers of the epidermis and intraepidermal clustering or nesting of large malignant melanocytes. Pagetoid cells may be disposed singly as high in the epidermis as the stratum corneum (Fig. 4). Cells nests are usually seen more basally within the epidermis. Occasionally the entire epidermis may be replaced by nests of melanocytes. While displaying obvious atypical features of enlarged nuclei and one or more prominent nucleoli, cells within nests usually have a distinct, rather monotonous epithelioid appearance. Frequently seen with light mi-
croscopy are tan granules within the cytoplasm of these cells, indicative of melanin formation. The above description is in contrast to the marked variability in the cell morphology from one melanocyte to the other as seen in lentigo maligna and lentigo maligna melanoma. When invasion occurs, the epithelioid appearance is usually preserved but cells may be present individually, in cords or strands, or in nests (Fig. 5). Invariably present is a dense inflammatory infiltrate composed of lymphocytes and other mononuclear cells but usually not polymorphonuclear leukocytes (1, 3).

Nodular Melanoma

In nodular melanoma, intraepidermal and dermal invasion are uniformly coexistent. Current methods of classification stipulate that if intraepidermal malignancy extends more than the width of three rete ridges beyond dermal invasion in any histological section examined, the lesion is superficial spreading melanoma. Frequently, a few or no intraepidermal malignant cells are seen (Fig. 6). Inflammatory cells are interposed between groups of invasive melanocytes in the dermis (Fig. 7). Clark et al. have correlated the small percentage of nodular melanomas with irregular gross outline with invasion limited to the papillary dermis. The majority of exophytic, berrylike, or dome-shaped nodular melanomas are invasive to Levels III,
FIG. 5. Superficial spreading melanoma. Intraepidermal melanocytes are present at the arrow with dermal invasion evident to left. Invasion was to Level III. Note the marked inflammatory infiltrate at the right. H&E, 100×.

FIG. 6. This demonstrates the invasive margin of a raised nodular melanoma. No malignant melanocytes are seen within the epidermis. Invasion was to Level IV. H&E, 40×.
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FIG. 7. This is the same case as in Fig. 6. The higher power shows many bizarre, occasionally multinucleated invading melanocytes. Note the interspersed inflammatory infiltrate at arrow. H&E, 250x.

IV, or V. When distinct intraepidermal malignancy is absent, the lesion should be distinguished clinically from a metastatic melanoma. The cells in nodular melanoma may be epithelioid, spindlelike, or smaller and nevuslike (Fig. 8). Nodular melanomas pathologically correlate well with their clinically proven aggressiveness in that bizarre nuclei, mitotic figures, and deep invasion are the rule (1, 3).

PATHOLOGY AND PROGNOSIS

Numerous authors have stressed the relationship of levels of invasion to prognosis (1, 4, 5). A large series of patients with melanoma of all types compiled by Clark et al. indicated survival rates in relationship to depth of invasion (1). These data are expressed in terms of percentage of patients who died secondary to metastatic tumor. Patients with invasion to Level II, III, IV, and V had mortality rates of 8.3, 35.2, 46.1, and 52%, respectively, within the follow-up period. A large group of patients with superficial spreading melanoma were similarly evaluated. Mortality rates were 9.1, 31.9, 40.5, and 50.0% for levels II–V, respectively. The biology of superficial spreading melanoma and lentigo maligna melanoma is similar in that early in their course they are superficial, slowly growing, centrifugally or laterally spreading lesions. Conversely, the natural history of nodular melanoma is rapid penetration and invasion from its inception. The statistical studies to date suggest that, regardless of the initial biological features and the gross topography, the survival rates among all
FIG. 8. This nodular melanoma was invasive to Level IV, almost to Level V. The spindle-cell morphology of these malignant cells is apparent. The reticular dermis is indicated by the arrow at the left. H&E, 250×.

types correlate best with the level of invasion noted at time of diagnosis. Therefore, accurate histopathological diagnosis and determination of depth of invasion remain today the most useful guides to further therapy and prognosis.

REFERENCES
1. Clark, W. H., From, L., Bernardino, E. A., and Mihm, M. C., The histogenesis and biological behavior of primary human melanomas of the skin. Cancer Res. 29, 705, 1969.
2. Clark, W. H., and Mihm, M. C., Lentigo maligna and lentigo maligna melanoma. Amer. J. Pathol. 55, 39, 1969.
3. Mihm, M. C., Clark, W. H., and From, L., The clinical diagnosis, classification and histogenetic concepts of the early states of cutaneous malignant melanoma. N. Engl. J. Med. 284, 1078, 1971.
4. McGovern, V. J., The classification of melanoma and its relationship with prognosis. Pathology 2, 85, 1970.
5. Mehnert, J. H., and Heard, J. L., Staging of malignant melanomas by depth of invasion: A proposed index to prognosis. Amer. J. Surg. 110, 168, 1965.