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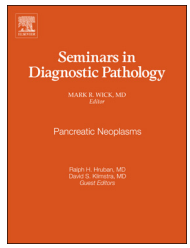

Cutaneous melanoma: A current overview

Mark R. Wick, MD

Division of Surgical Pathology, University of Virginia Health System, Room 3020, 1215 Lee St, Charlottesville, Virginia 22908-0214

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ABSTRACT

Cutaneous melanoma continues to increase in frequency, for unknown reasons, and it can pose considerable diagnostic challenges to clinician and pathologists alike. This review considers current concepts pertaining to that tumor, including those concerning epidemiology, clinical diagnosis, histologic findings, adjunctive diagnostic studies, and prognosis.

Inexplicably, the worldwide incidence of melanoma has increased over the past 10 years.[1] In the United States, that neoplasm comprises 3–5% of new skin cancers each year, but it causes 65% of all deaths that are attributable to cutaneous malignancies.[2] Internationally, the annual total of deaths associated with melanoma is approximately 50,000.[3] Whether unprotected sun exposure is a risk factor for melanoma continues to be debated, but scientific opinion does support such an association.[4]

This article discusses the major clinical and pathologic features of primary cutaneous melanoma. Summarized comments on therapy are also included.

Historical, epidemiological, and clinical features of cutaneous melanoma

Historical information

Rene Lannaec first described mucocutaneous melanoma in the medical literature in 1806, as a distinct entity.[5] In 1821, Norris[6] further elaborated on its features and he contributed additional observations regarding its biology over the following 40 years. It was recognized that melanoma could show a familial pre-disposition, and a possible association between fair skin and sun exposure was delineated as well. Finally, a biological kinship between melanoma and ordinary melanocytic nevi emerged. Norris recognized that melanoma could be pigmented or amelanotic, and that it sometimes metastasized prodigiously to the viscera. The latter circumstance was recognized as hopeless, and it was therefore empirically recommended that primary cutaneous melanoma should be removed surgically with a generous cuff of uninvolved tissue in an attempt to "interdict" metastasis.[7]

With the advent of "academic" surgery in the 1890s, an increasingly aggressive approach to melanoma therapy began and quickly flourished. "Radical" excision of cutaneous melanoma—including infratumoral soft tissue—was implemented, along with prophylactic removal of all regional lymph nodes.[8,9] Dr. William Halsted had popularized that approach for the treatment of breast cancers in the late 19th century, and it was extended to include several other tumor types as well. This philosophy eventually culminated in forequarter or hindquarter amputations in the management of melanomas with "in transit" metastases.

Subsequently, during the 1970s and 1980s, randomized studies were done to address the long-term efficacy of complete lymphadenectomies in melanoma cases.[10–12] Overwhelmingly, those assessments showed no statistically significant augmentation of tumor-specific survival that could be attributed to lymph node clearance. Concomitantly, other evaluations concluded that melanomas measuring <0.76 mm in depth could be excised successfully using 1 cm surgical margins, with no increment in local recurrence or metastasis.[13]

Despite those data, the current surgical management of melanoma still includes regional lymphadenectomy, as tied

E-mail address: mrwick1@usa.net

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to the result of a "sentinel" lymph node biopsy.[14] The validity of that regime has been challenged, on the basis of both pathobiological and empirical clinical information.[15,16]

Epidemiological factors

Epidemiological studies have linked exposure to UVA and UVB ultraviolet light with the risk of developing melanoma via damage to the nucleic acid of melanocytes in the skin.[17] The risk is also apparently influenced by socioeconomic status, a young age at which excessive sun exposure first occurs, and the level of endogenous skin pigmentation; fair-skinned and red-haired individuals have a greater susceptibility.[18] Families with the "dysplastic nevus" or "atypical mole" syndrome (AMS) and persons with "giant" congenital melanocytic nevi also have an increased risk of developing melanoma.[19,20] Patients with a personal history of primary melanoma are also more likely to develop other similar tumors.[18,20]

Clinical diagnosis

Visual examination is still the most efficient procedure for the clinical identification of cutaneous melanoma, particularly if it is coupled with targeted biopsy procedures. Pigmented lesions with an irregular color or shape are the principal concern. A straightforward method for identifying melanoma is associated with the mnemonic "ABCDE," for asymmetry, irregular borders, variegated color, diameter >6 mm, and progressive lesional enlargement.[21,22] Dermoscopy has been used in the last decade as a diagnostic aid. Persons with fair skin and blond or red hair have an increased risk for development of amelanotic melanomas, and it is in that context that dermoscopic evaluation is especially useful.[23,24]

Whole-body photography is utilized in the sequential surveillance of high-risk patients who have multiple pigmented skin lesions, particularly in the setting of the AMS.[25] That procedure is best coupled with dermoscopy, and the both together yield a high rate of detection.

Biopsy procedures used in possible melanoma cases should be excisional in nature, if at all feasible. Shave, punch, and even limited incisional tissue sampling often distort the histological appearance of the lesion and can obfuscate important prognostic microscopic features.[26–32] If a pigmented lesion warrants enough concern to biopsy it at all, one must use proper procedure.

Histologic features of cutaneous melanoma

Melanomas are well-known as histological pretenders—particularly their amelanotic variants—and they therefore enter into the differential diagnosis of many other cutaneous lesions. Unusual variants of non-pigmented melanoma include small-cell, clear ("balloon")-cell, sarcomatoid, signet-ring-cell, rhabdoid, myxoid, hemangiopericytoma-like, and pseudoglandular entities. Those subtypes have been considered in detail elsewhere,[33–36] and are only referenced here in the interest of concision. The ensuing discussion considers the main histological patterns that are seen in melanomas of the skin.

General histological characteristics of cutaneous melanoma

Systematic attention to several histologic features is necessary in the evaluation of any melanocytic lesion. They include lesional symmetry, confluence of cellular growth at the epidermal base (EB), the extent of intracellular cohesion, peripheral lesional demarcation, nuclear pleomorphism and hyperchromasia, the number and placement (superficial or deep) of dermal mitotic figures in the tumor, the size of melanocytic cellular nests at the EB and in the dermis, and so-called "maturation" (decreasing cellular and nuclear size) in a comparison of the superficial and deep portions of the proliferation.[17,37–47]

Generally speaking, asymmetry, confluent growth, upward (pagetoid) cellular disposition above the EB with "consumption" of the epidermis, intralesional dyshesion, nuclear aberration, indistinct peripheral demarcation, deep mitotic activity, and "clonal" cell nests (>10 cells in maximum dimension) are more often seen in melanoma than in nevus variants (Fig. 1). Other secondary findings in melanoma cases may include a lichenoid tissue reaction[48] (Fig. 2), regression—with dermal fibrosis, pigment incontinence, and scant lymphoid inflammation[49] (Fig. 3)—and intralesional pigment that is dispersed, grey–brown, and intracytoplasmic.[50]

None of these observations is sufficient in isolation to distinguish benign from malignant melanocytic tumors. One must make a mental list of them while examining any given lesion, eventually providing the basis for an overall interpretative impression. That process sounds rather imprecise, and it is. Such limitations likely account for the relatively poor interobserver reproducibility that is associated with the histologic diagnosis of melanocytic proliferations.[51–54]

Superficial spreading (pagetoid) melanoma

Superficial spreading melanoma (SSM) is the commonest form of that neoplasm. It manifests an excess of melanocytes in the epidermis, cytological atypia, upward spread of the tumor cells into the suprabasal surface epithelium, and epidermal "consumption" with or without dermal infiltration[55–57] (Fig. 4). The intraepidermal cells may be grouped in small clusters or dispersed singly, often with a "buckshot" distribution. As a consequence, SSM shows a microscopic similarity to Paget's disease and pagetoid squamous cell carcinoma *in-situ* (SCCIS) (Fig. 5). When pagetoid melanoma is non-pigmented, histochemical, and immunohistochemical techniques are used to resolve the cited differential diagnosis. SSM is reactive for S100 protein and melan-A, whereas the other two alternative lesions are not.[58] Some examples of Paget's disease and SCCIS contain tumor cells that are positive with the Fontana–Masson method for melanin,[59,60] but that finding is certainly more typical of melanomas.

Lentiginous melanoma

Lentiginous melanomas (LMs) are characterized histologically by confluent growth of atypical melanocytes at the EB.[61–66] They arise in sun-exposed skin and on the distal extremities;