Melanoma

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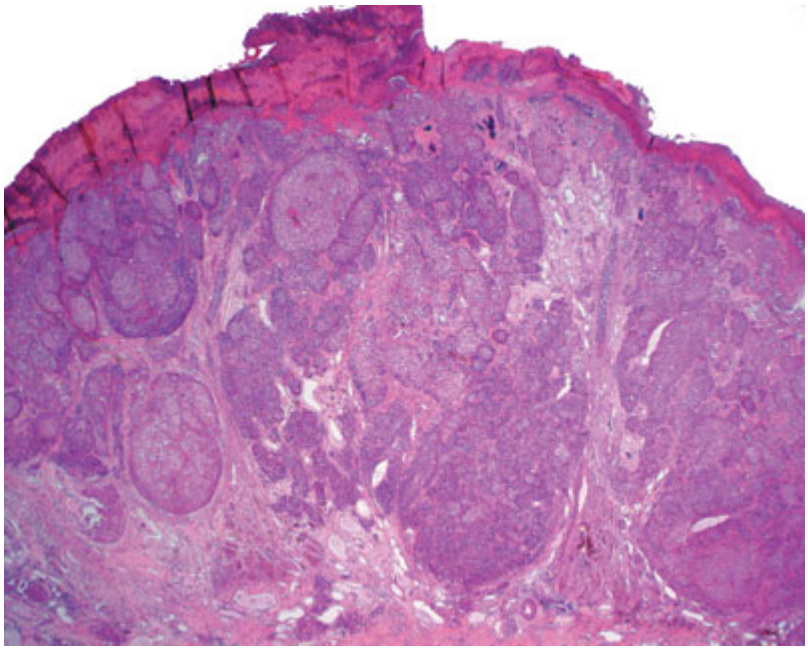

Figure 1. A large melanoma exhibits the typical surface ulcera-tion and asymmetry. Numerous expanded nests and individual cells can be seen filling and expanding both the papillary and reticular dermis. Pigment and inflammation are also visible.

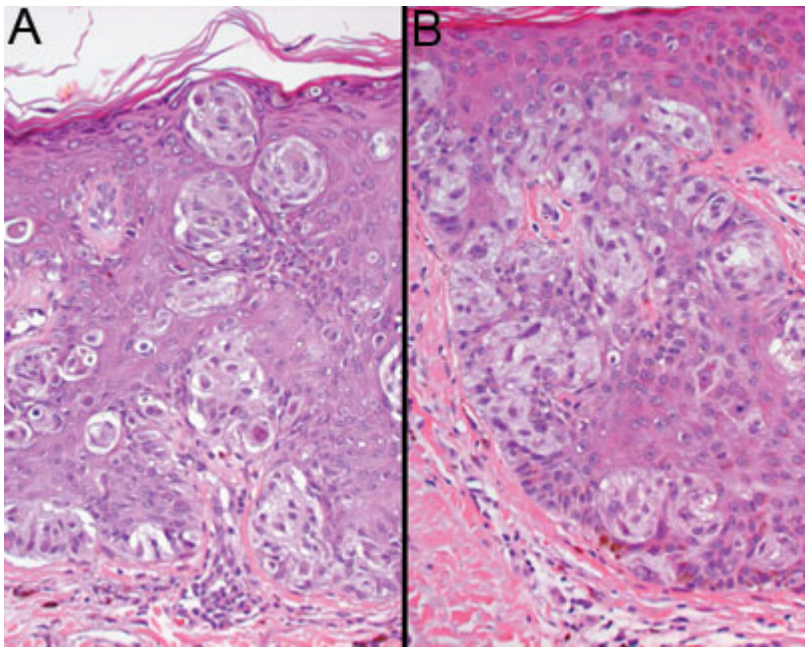

Figure 2. ***A:*** *Melanoma in situ is defined in part by single atypical melanocytes, nests, and migration of melanocytes above the basal zone (pagetoid spread).* ***B:*** *Feature of melanoma is extension of the atypical cells down adnexal structures.*

Melanoma is a malignancy of melanocytes that show a series of molecular events that result in the melanocytes going through a stepwise progression from dysplasia to invasion to metastasis. Melanomas account for approximately 4.4% of all malignancies. Approximately 62,000 new cases of melanoma are reported annually in the United States, and they are responsible for about 7,900 deaths. The incidence of melanoma worldwide has been increasing steadily.

The vast majority of melanomas develop on sun-exposed areas of the skin (topographic differences exist between the sexes), but acral, ocular, mucosal, and solid organ melanomas are not uncommon. The greatest percentage of mucosal melanomas occur in the head and neck area (~55%, although these are not discussed in this installment of Pathology Clinic). Skin melanoma is more common in whites than blacks (>10:1) and in men than women. It is most common in the middle and later decades of life, although patients of all ages have been affected.

At presentation, patients usually report a new skin growth or a change in the size, shape, or color of an existing “mole.” The usual warning signs are expressed in the “ABCD” mnemonic: asymmetry, border irregularity, color change, and a diameter of greater than 6 mm. Risk factors for skin melanoma include a previous diagnosis, a family history, sun sensitivity, excessive sun exposure, fair skin and red hair, an immunosuppressive disease, and certain occupational hazards (e.g., exposure to arsenic or creosote).

Melanomas arise from melanocytes, which are the melanin-producing cells of the skin. The neoplasm affects the junction of the epidermis and dermis, in which there is a irregular expansion in the number of melanocytes and a disordered architectural arrangement. Histologically, melanomas are usually large lesions that exhibit an irregular silhouette and a lack of symmetry, showing isolated nests and individual cells at the periphery, often extending along the junction for quite a distance (figure 1). Sometimes a residual benign nevus is present, which hinders the pathologist’s ability to accurately determine where the melanoma ends and the nevus begins. Several prognostic histologic features may be present, including surface ulceration, an inflammatory infiltrate at the advancing dermal border, desmoplastic fibrosis, regression (i.e., fibrosis, granulation-tissue–type vessels, and pigment-laden histiocytes), and vascular invasion. Compared with benign nevi, melanoma is more likely to be associated with a confluence of atypical single cells, nests of various sizes and shapes, and migration of the melanocytes above the basal zone into the upper layers of the epidermis or extension down adnexal structures (pagetoid spread) (figure 2).

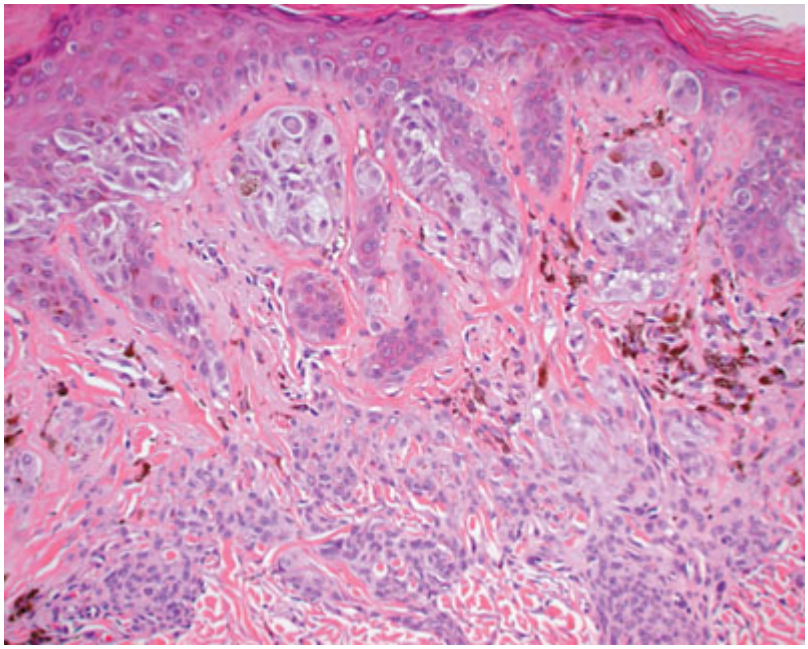

Figure 3. The typical melanocytes are associated with desmoplastic stroma in the dermis. Pigment is present, and cellular pleomorphism is noted.

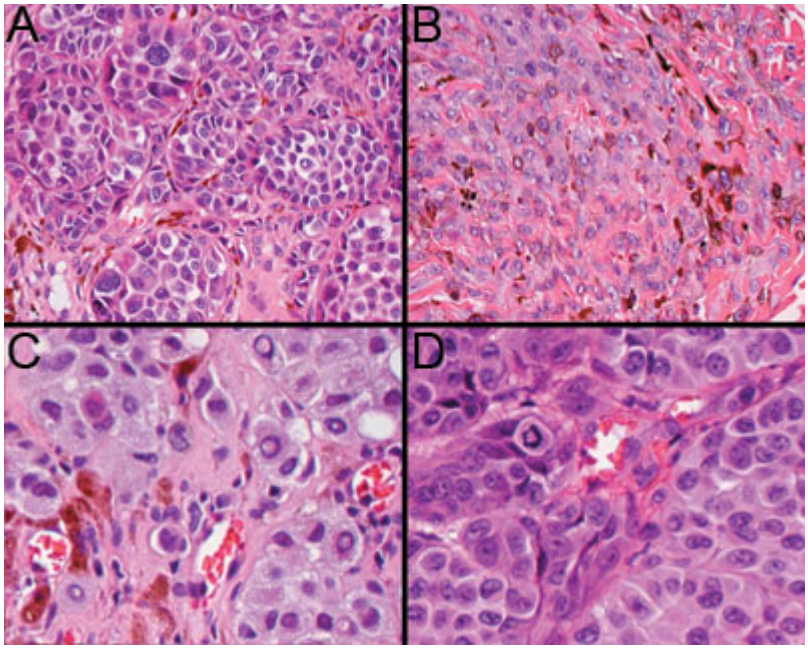

*Figure 4. These images show a number of features seen in melanoma, including nuclear pleomorphism (**A**), desmoplastic stroma with intracellular pigmentation (**B**), intranuclear cytoplasmic inclusions (**C**), and increased mitotic figures (**D**).*

The melanocytes invade into the dermis (vertical-growth phase) in a variety of architectural patterns, including nested, fascicular, solid, organoid, storiform, peritheliomatous, and papillary, to name just a few (figure 3). Pigment may be present within the tumor cells or picked up by macrophages in the stroma, although amelanotic melanomas are seen. Mitotic figures, including atypical forms, are usually easy to find. The neoplastic cells are protean, ranging from small cells with a high nucleus-to-cytoplasm ratio to remarkably pleomorphic cells with abundant cytoplasm. The cells can be undifferentiated, epithelioid, spindled, plasmacytoid, rhabdoid,

giant-cell, or polygonal. The nuclei contain dense, coarse nuclear chromatin and prominent, irregular eosinophilic nucleoli; they frequently show intranuclear cytoplasmic inclusions (figure 4).

Breslow's depth of invasion (measured in hundredths of a millimeter) and *Clark's level of invasion* into the layers of the dermis (papillary dermis, reticular dermis, and subcutaneous layer) are both important components of the diagnosis, as they guide therapy and yield prognostic information. Immunohistochemistry stains (S-100 protein, HMB-45, melan-A, and tyrosinase) can help confirm the melanocytic nature of the tumor, but the histologic features of malignancy must be present to make the diagnosis of melanoma. The term *melanoma in situ* is used when the basement membrane of the epidermis is not penetrated by the melanocytes (about 50,000 such cases occur yearly in the U.S.). Needless to say, there are several patterns and histologic subtypes that are clinically important (e.g., desmoplastic melanoma, nevoid melanoma, and spindle-cell melanoma).

Most melanomas (>80%) are detected early (in situ disease or limited depth of invasion), and the prospects for long-term survival are excellent (5-yr survival: 98%). However, if regional disease (metastasis to the local lymph nodes) develops, survival decreases (5-yr survival: 64%). The prognosis is much worse in cases of distant metastasis (5-yr survival: 16%).

Prompt surgical excision, including a margin of uninvolved skin, followed by a sampling of the draining lymph nodes (sentinel lymph node) for staging, is the initial mainstay of therapy. Advanced disease is managed with multimodal therapy, but results have been mixed. Early detection by regular skin examinations and microscopic examination of all suspicious lesions is essential.

Suggested reading

Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 1: Epidemiology, risk factors, screening, prevention, and diagnosis. Mayo Clin Proc 2007;82(3):364-80.
Markovic SN, Erickson LA, Rao RD, et al. Malignant melanoma in the 21st century, part 2: Staging, prognosis, and treatment. Mayo Clin Proc 2007;82(4):490-513.
Miller AJ, Mimh MC Jr. Melanoma. N Engl J Med 2006:355(1):51-65.

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