Spitzoid Melanoma

52

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Introduction

Spitzoid melanoma is a controversial melanocytic malignant neoplasm. Although the 2009 Workshop of the International Melanoma Pathology Study Group has discouraged the usage of this term until this subset of melanomas can be more rigorously defined by phenotypic and genetic studies, spitzoid melanoma is still used to describe melanomas with architectural and/or cytologic features resembling Spitz nevus. Spitzoid melanoma indeed seems not to have its own distinguishing features but is defined in comparison with Spitz nevus, especially from a histological point of view.

Clinical Features

Spitzoid melanoma is considered a melanoma subtype often developing in children, while it seems to be more common in adults. The neoplasm is characterized by a changing nodule that can be amelanotic, pigmented, or variegated in color (Fig. 52.1), crusted, and ulcerated, often reaching 10 mm or more in diameter. The head and extremities are the most frequent involved sites in the childhood type. Female predominance occurs in spitzoid melanoma.

Pathology

Spitzoid melanoma shares many histopathologic features with Spitz nevus, and it is one of the most difficult and problematic diagnoses in dermatopathology. The mainstay for the diagnosis is nests of variable size and shape with large spindle or epithelioid cells characterized by abundant eosinophilic cytoplasm and prominent eosinophilic nucleoli. Although there are no specific histopathologic diagnostic criteria for spitzoid melanomas, these malignancies are usually asymmetrical, lack both circumscription and maturation, and exhibit high cell density, deep mitoses, an expansive growth pattern and consumption of the epidermis or ulceration (Figs. 52.2–52.6).

Compared to Spitz nevus, the melanocytic epidermal component is usually not well demarcated with spreading of melanocytes at the edges. The junctional nests are irregularly shaped and unevenly distributed with irregular pseudoacantholytic clefts, and in some areas, single melanocytes predominate showing a pagetoid spreading (Fig. 52.3). The dermal component is characterized by an asymmetrical nodular proliferation of irregular and crowded nests with enlarged, atypical epithelioid or spindle-shaped melanocytes that are often amelanotic and lack maturation (Figs. 52.4 and 52.5).

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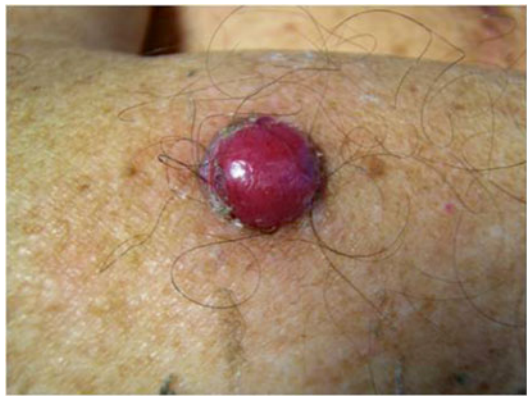

Fig. 52.1 Spitzoid melanoma. An erythematous fast-growing nodule on the upper arm of a 49-year-old man

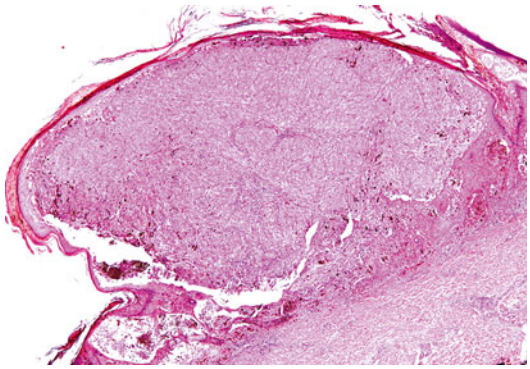

Fig. 52.2 Spitzoid melanoma. An asymmetrical, expansive nodule showing high cell density and consumption of the epidermis

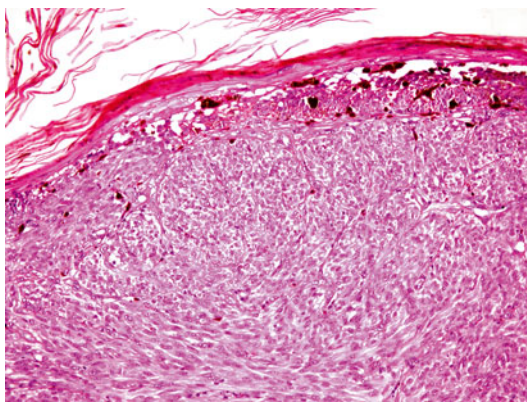

Fig. 52.3 Spitzoid melanoma. A spindle-shaped and epithelioid eosinophilic proliferation. The junctional nests are irregularly shaped and unevenly distributed with irregular pseudoacantholytic clefts

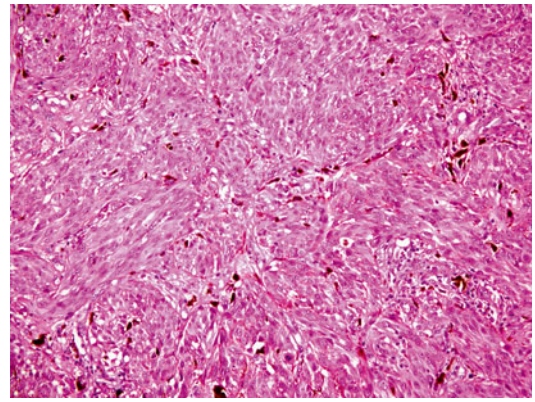

Fig. 52.4 Spitzoid melanoma. The dermal component is characterized by a nodular proliferation of irregular and crowded nests with enlarged, atypical epithelioid, or spindle-shaped melanocytes lacking maturation

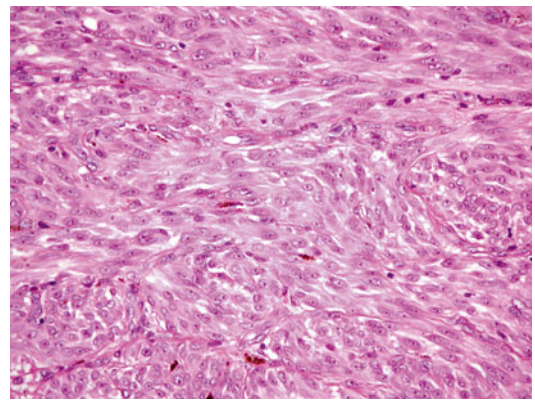

Fig. 52.5 Spitzoid melanoma. Atypical epithelioid or spindle-shaped melanocytes with abundant eosinophilic cytoplasm and prominent eosinophilic nucleoli. Deep mitoses are present in the deep dermal component

The phenomenon of zonation (similar appearance of melanocytes along horizontal levels of the lesion) is usually absent. Spitzoid melanoma has a higher degree of cytologic atypia with more pleomorphic, hyperchromatic nuclei that contain large or multiple nucleoli (Figs. 52.7 and 52.8). The deep dermal component shows an expansile growth that involves the superficial subcutaneous tissue rather than an infiltrative pattern. Melanocytes in mitosis are an important clue; more than three dermal mitoses per high-power field, mitoses in the deeper parts of the lesion, and atypical mitoses favor a diagnosis of spitzoid melanoma. The epidermis may

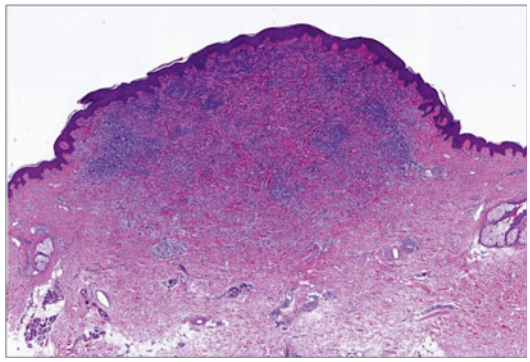

Fig. 52.6 Spitzoid melanoma. Another asymmetrical dermal-based tumor (Courtesy of H.Kutzner, Friedrichshafen)

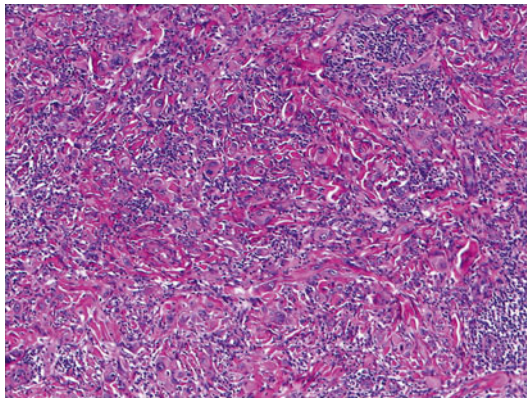

Fig. 52.7 Spitzoid melanoma. This spitzoid melanoma has a higher degree of cytologic atypia with lack of maturation and a dense "brisk" lymphoplasmacytic infiltrate

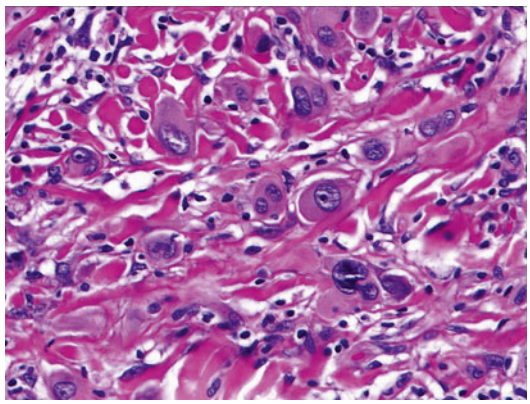

Fig. 52.8 Spitzoid melanoma. Spitzoid melanocytes have a higher degree of cytologic atypia with more pleomorphic, hyperchromatic nuclei that contain large or multiple nucleoli

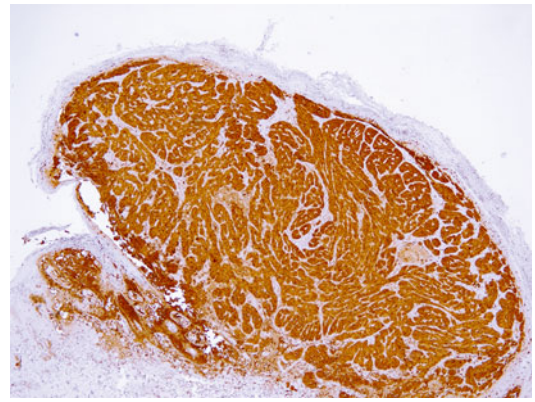

Fig. 52.9 Spitzoid melanocytes are positive for HMB45

ulcerate or is atrophic showing epidermal consumption. Kamino bodies are not features of spitzoid melanoma, and when they are present in a spitzoid neoplasm, a diagnosis of nevus is favored. A dense inflammatory lymphoplasmacytic infiltrate, lack of adnexal structures, areas of necrosis, solar elastosis, regression with or without melanosis, vascular invasion, and neural infiltration all are features that favor melanoma. Recently, five subtypes of spitzoid melanoma have been suggested, i.e., "genuine" similar to small compound Spitz nevus, "uniform" including intradermal spitzoid neoplasm composed of a sheet of epithelioid cells with radical absence of adnexal appendages and little or any collagen, "packed" including intradermal spitzoid neoplasm with very compact nests and dermal artifactual breakages, "polypoid," and "pigmented" including compound spitzoid neoplasm with striking amounts of melanin both in superficial and deep dermis with irregular distribution and melanophages.

While no specific immunohistochemical marker or molecular and genetic test still exists to distinguish Spitz or spitzoid benign neoplasm from spitzoid melanoma, a combination of immunohistochemical stains has been proposed as a useful tool. This panel includes HMB45, (Fig. 52.9), Ki-67/MIB-1, CD99, p16, Neuropilin-2, Bcl-2, cyclin D1, p53, and p21 among others (Figs. 52.6, 52.7, 52.8 and 52.9). HMB45 is evaluated according to a maturation gradient. If the immunostain is expressed

throughout all of the lesion or in a patchy distribution to include deep melanocytic nests, this is considered a sign of malignancy. If there is positive staining at the top of the lesion with loss of staining in the deeper part into the dermis, this favors Spitz nevus. Ki-67/MIB-1 is suggested to be a useful marker in thick and noninflammatory neoplasms and a nuclear proliferation index of 10 % favors a diagnosis of melanoma. CD99 is reported to be expressed in 56 % of spitzoid melanomas in a strong and diffuse pattern but only in 5 % of Spitz nevi. Loss of both cytoplasmic and nuclear expression for p16 is present in spitzoid melanomas as compared with Spitz nevus without any correlation with its Breslow thickness. However, the value of p16 expression has been recently questioned as loss of p16 staining does not necessarily reflect malignancy, at least in spitzoid melanoma of adulthood type. Neuropilin-2 is a cytoplasmic/cell surface protein that is a mediator of melanoma-endothelial cell interaction and has been found to be expressed by spitzoid melanoma, while most Spitz nevi are negative. A wider number of cases and a long-term follow-up are needed to determine whether immunohistochemistry has any predictive value in the evaluation of spitzoid lesions.

As for molecular diagnostic studies, spitzoid tumors and melanoma usually show different genetic profiles. Chromosomal aberrations were detected in a higher percentage of cases of spitzoid melanoma by FISH analysis, but this finding deserves further validation. Recently, increased sensitivity for detection of malignant spitzoid neoplasms using 9p21 FISH has been described, and cases with homozygous 9p21 deletions seem to have the greatest risk of malignant biological behavior.

Array comparative genomic hybridization (aCGH) has demonstrated that 76 % of Spitz nevi had no DNA copy changes, while the remaining subset had a gain involving the entire p-arm of chromosome 11 corresponding to expression of the HRAS gene. On the other hand, HRAS is rarely mutated in malignant melanoma, which in contrast can have multiple copy gains in chromosomes 7, 8, 6p, and 1q and/or deletions in chromosomes 9p, 10q, 6q, and 8p (22 %) and can have mutations in B-RAF and N-RAS.

Differential Diagnosis

Clinically, spitzoid melanoma resembles hemangioma, pyogenic granuloma, xanthogranuloma, or basal cell carcinoma. The histopathologic spectrum of spitzoid melanocytic proliferations includes typical Spitz nevus, Spitz tumor, atypical Spitz tumor, and spitzoid melanoma arising de novo. There is no single specific criterion and the diagnosis relies on a good clinical, histopathologic, immunohistochemical, and molecular profile correlation (see section "Pathology"). Lesions that cannot be definitively classified are referred to as atypical spitzoid neoplasms that are a provisional diagnostic category rather than a definitive diagnosis.

Prognosis

The prognosis of spitzoid melanoma is the same as that for other variants of melanoma of equal Breslow thickness. However, the prognosis seems also to be related to the age of the patient; in fact, children aged 17 years or younger with spitzoid melanomas have a better prognosis than adults, even when they have local metastases. The hypothesis that spitzoid melanomas in childhood and adulthood are biologically different deserves further studies. The 5-year survival rate was 88 % when arising in patients between age 0 and 10 years compared with 49 % in patients aged 11–17 years.

Treatment

Spitzoid melanoma must be treated following the same guidelines as for other types of melanoma, which is based on Breslow tumor thickness, ulceration, and mitotic figures. Melanomas in situ must be excised with 0.5 cm margin of noninvolved skin; for invasive melanomas of less than 1 mm in thickness, the margin is 1 cm; for 1–2 mm in thickness, the margin is 1–2 cm; and for melanomas 2–4 mm in thickness, the recommended margin is 2 cm. As for sentinel lymph node biopsy (SLN), spitzoid melanoma follows the same

guidelines as the other types of melanomas. The SLN biopsy is only for prognostic purposes and is not intended to be therapeutic. If the SLN is positive, complete lymph node dissection is performed.

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