Common Spindle Cell Malignant Neoplasms of the Skin: Differential Diagnosis and Review of the Literature

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Citation

Abstract
Malignant and borderline-malignant neoplasms of the dermis can pose diagnostic challenges. Because these tumors can share similar clinical and histologic features, including a predominantly spindle cell morphology, the pathologist must be familiar with these entities in order to facilitate accurate diagnosis, as treatment for these tumors may be different. We review several of these lesions with respect to clinical and histologic features: desmoplastic melanoma, spindle cell carcinoma, spindle cell atypical fibroxanthoma, dermatofibrosarcoma protuberans, and cutaneous leiomyosarcoma.

INTRODUCTION
While malignant spindle cell neoplasms of the dermis are relatively rare tumors, they occur with enough frequency that the practicing pathologist must be adept at recognizing such tumors and making accurate diagnoses, as treatment of these various lesions may be disparate. That being said, however, differential diagnosis can be extremely difficult, with each lesion showing overlapping clinical and histologic features. Fortunately immunohistologic analysis greatly aids in the diagnostic process. We describe five malignant spindle cell neoplasms of the dermis encountered by the practicing pathologist and review clinical and diagnostic features of each, with the aim of providing a practical guide for the general surgical pathologist.

DESMOPLASTIC MELANOMA

CLINICAL FEATURES
Desmoplastic melanoma (DM) is a rare variant of spindle cell melanoma and an uncommon form of melanoma, comprising 4% of all melanomas. DM was first described by Conley et al. in 1971 as an inconspicuous superficial melanocytic lesion of the head and neck, preceding the development of a bulky dermal and subcutaneous tumor [1]. The tumor presents in older individuals as a flesh-colored or variably pigmented nodule measuring on average 2 cm. It is usually seen on sun-exposed skin (37%) but also on mucosal and acral sites. Males are affected more often than women, with the exception of the lower limbs. If prominent neurotropism is present, which occurs in at least 30% of cases, nerve invasion can produce dysesthesias or nerve palsies. DM often is difficult to detect clinically, since half lack pigmentation. Pale lesions, in particular, are mistaken clinically for basal cell carcinoma, dermatofibroma, or scar. Pigmentation often is due to an associated lentigo maligna or superficial spreading melanoma. Unusual presentations include young age, an erythematous nodule, or alopecia. Ulceration is uncommon.

HISTOPATHOLOGY (FIGURES 1, 2, 3, 4)
DM is composed of usually non-pigmented fusiform melanocytes which often resemble fibroblasts (Figure 1). The atypical melanocytes are embedded within collagen bundles and may be associated with mild to marked stromal fibrosis. Phenotypical heterogeneity is under-recognized and desmoplasia may be seen throughout the tumor or in combination with conventional melanoma (“combined” DM) [3, 4]. Ultrastructurally, the desmoplastic component appears to derive from melanocytes that have undergone adaptive fibroplasia [2]. Most often the spindle cells are arranged in a haphazard fashion, but are sometimes arranged in parallel bundles or in storiform configurations. The spindle cells are usually mildly to moderately atypical, although cells with larger, more hyperchromatic nuclei are often seen. Paucicellular variants of DM, in particular, are easily missed on small biopsy specimens. Junctional components are sometimes minimal or absent. Mitotic rate is variable but often is low, with abnormal forms in the more cellular tumors. The overlying epidermis may be thinned or thickened with clusters of lymphocytes located at the tumor periphery. Neurotropism is a common feature (seen in up to
30%) and neural differentiation with a malignant peripheral nerve sheath-like histology may be seen [5-8]. Neurotropism may be peri- or intraneural and may extend beyond the desmoplastic component. An osteogenic variant has been reported [9].

The spindle cells in DM are positive for S-100 protein (Figure 2), although sometimes within only a few nuclei (Table 1). Neuron-specific enolase (NSE) and smooth muscle actin (SMA) may be positive, while HMB45 (Figure 3) and Melan-A (MART-1) and are usually negative [10-13]. Microphthalmia transcription factor (MITF) may (Figure 4) or may not be positive. No single specific marker is yet available to differentiate desmoplastic melanomas from other tumors [14].

**Figure 1**
Figure 1. Dermal spindle cell neoplasm.

**Figure 2**
Figure 2. The tumor cells are focally positive for S-100 protein.

**Figure 3**
Figure 3. Tumor cells are negative for HMB-45.

**Figure 4**
Figure 4. Tumor cells show strongly positive nuclear stain with MITF.

**PROGNOSIS AND TREATMENT**
Desmoplastic melanoma was reported in the older literature as having a worse prognosis when compared to other types of melanoma. However, recent findings suggest that prospectively diagnosed and definitively treated lesions show the same survival rate as the usual forms of melanoma when various histologic parameters and risk factors are controlled. Expression of N-cadherin may portend a poorer prognosis, however [15]. Treatment is with wide local excision.

**SPINDLE CELL (SQUAMOUS CELL) CARCINOMA.**
CLINICAL FEATURES

Squamous cell carcinoma is the second most common cutaneous malignancy after basal cell carcinoma. The uncommon spindle cell variant occurs commonly on sun-exposed surfaces of elderly patients as a plaque or as an enlarging tan to red nodule, often with surface ulceration and crusting. The spindle cell (squamous cell) carcinoma (SCSCC) may be associated with previous skin injury, including trauma and radiotherapy.

HISTOPATHOLOGY (FIGURES 5, 6, 7, 8)

Four histopathologic categories of squamous cell carcinoma are described: conventional, spindle cell, acantholytic, and verrucous. In the uncommon spindle cell variant, atypical spindle cells emanate from the epidermis and form whorls intermingling with strands of collagen (Figures 1, 2). Within the dermis, the cells form intertwining fascicles and bundles. Individual tumor cells have indistinct borders and contain eosinophilic cytoplasm. Nuclei are hyperchromatic or vesicular and elongated. Nuclei may be pleomorphic and contain multiple nucleoli. Mitotic activity is brisk and atypical forms may be seen. With cellular pleomorphism and tumor giant cell formation, the tumors can bear a close resemblance to atypical fibroxanthoma. In fact, prior to the advent of immunohistochemistry, these lesions were often misdiagnosed. Connection of malignant tumor cells to the epidermis or foci of more typical squamous differentiation favor spindle cell carcinoma. Cytokeratin stains (Figure 7) are usually helpful. In addition, SCSCC can stain positively with mesenchymal markers such as vimentin (Figure 8) and smooth muscle actin.

Recently it has been suggested that p63 may be a useful marker for SCSCC; Dotto et al. reports a series of 13 cases of SCSCC in which nuclear expression was seen in all cases, while focal labeling was seen in only 2/4 cutaneous leiomyosarcomas and 2/10 atypical fibroxanthomas [16].

Figure 5

Figure 5. Ulcerating tumor infiltrates into the dermis and is composed of solid nests of squamoid cells as well as pleomorphic spindle cells.

Figure 6

Figure 6. The squamoid cells blend into the spindle cells
Figure 7
Figure 7. Both epithelial and spindle cells are positive for CK AE 1/3 (Cytokeratin).

Figure 8
Figure 8. Both epithelial and spindle cells are positive for Vimentin.

PROGNOSIS AND TREATMENT
Spindle-cell squamous cell carcinoma is a poorly differentiated variant of squamous cell carcinoma with the potential for an aggressive clinical course. One-third of cutaneous squamous cell carcinomas that metastasize are of this type. Treatment is surgical. Metastases usually first occur to the regional lymph nodes.

SPINDLE CELL ATYPICAL FIBROXANTHOMA. CLINICAL FEATURES
Atypical fibroxanthoma (AFX) usually arises in sun-exposed skin of the head and neck in older patients, often on the nose and cheek. Therapeutic radiation is a predisposing factor, with tumors usually appearing more than a decade following treatment. AFX usually presents as a nodule, which is sometimes ulcerated. The surface may be reddened and polyoid, resembling a capillary hemangioma.

HISTOPATHOLOGY (FIGURES 9, 10)
AFX is a highly cellular mesenchymal tumor. There is an extensive proliferation of spindled to polygonal cells (Figures 9 and 10), which in the usual form closely resemble malignant fibrous histiocytoma (MFH) of the deep soft tissues. AFX are expansile, dermal nodules that may reach the epidermis causing pressure atrophy. Often there is a connection to the overlying epidermis. In other cases, an uninvolved portion of overlying dermis, or grenz zone, is present. In addition, the tumor can compress skin appendages laterally. AFX does not extensively involve the subcutis and does not invade deeper structures. Areas adjacent to the lesion may show solar elastosis, vascular dilation, and capillary proliferation. Hemorrhage can be extensive, with the associated presence of hemosiderin-laden macrophages. Scattered inflammatory cells can be seen. In contrast with the usual type of AFX, the spindle cell variant is not pleomorphic, although most cases contain scattered giant cells of varying proportion [17, 18]. Sclerosis may be prominent and the lesion may be active mitotically. This morphology creates diagnostic difficulties because of its resemblance to other malignant spindle cell tumors. An absence of junctional nesting argues against malignant melanoma, although caution must be taken as some spindle cell desmoplastic melanomas lack a junctional component.

Differentiation from spindle cell melanoma is suggested by lack of an overlying in-situ melanoma component and absence of S-100 staining in tumor cells. The cells of AFX are HMB-45 negative (Table 1). Spindle cell carcinomas show positive staining for cytokeratin and often keratinocyte dysplasia or Bowen’s disease is present at the edge of the lesion. Leiomyosarcoma can be confused with this variant of AFX. AFX, however, is desmin negative and shows only focal actin positivity. The neoplastic cells of AFX are positive for vimentin and CD68 (Figure 11). Matthew et al. reported CK117 positivity in 15/16 AFX, suggesting that c-kit may be a sensitive marker [19].
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Figure 9
Figure 9. Diffusely infiltrating dermal tumor.

Figure 10
Figure 10. The tumor is composed of predominantly pleomorphic polygonal cells.

Figure 11
Figure 11. Tumor cells show positivity with CD68 immunostain.

PROGNOSIS AND TREATMENT
Although AFX may be indistinguishable from MFH histologically, the prognosis is excellent following conservative excision. Most authors agree that larger tumors (>2 cm) which extensively invade subcutaneous tissue such as fascia or muscle, or show necrosis or vascular invasion, should be diagnosed as MFH. Lack of H-ras and K-ras mutations in AFX but presence in MFH further suggest biologic differences between these two entities [20].

DERMATOFIBROSARCOMA PROTUBERANS
CLINICAL FEATURES
Dermatofibrosarcoma protuberans (DFSP) is a neoplasm regarded as a superficial low-grade sarcoma. The lesion most commonly presents in young to middle-aged persons on the trunk or proximal extremities as an indurated plaque with one or more associated gray-white nodules. DFSP presents less often at other body sites, including the head, neck, and distal extremities [21, 22]. Early lesions are sharply-demarcated or plaque-like, often with peripheral red or blue discoloration. At this stage, lesions may clinically resemble morpheaform basal cell carcinoma. Advanced lesions are fungating and ulcerated. Sometimes the tumors contain gelatinous or translucent areas corresponding microscopically to myxoid change. Hemorrhage and cystic degeneration can occur.

DFSP exhibits slow and persistent growth, often over several years. There is evidence that many tumors develop during childhood and become clinically apparent later in life. Congenital and childhood forms are known, but may not
come to attention early because of difficulty in clinical detection [23-25].

**HISTOPATHOLOGY (FIGURES 12, 13, 14)**

DFSP shows a dense proliferation of monotonous spindle cells that diffusely infiltrate the dermis and subcutis (Figure 12). The center of the tumor is composed of slender fibroblasts which contain moderately-enlarged, tapered nuclei and are arranged around inconspicuous vessels in a distinctive storiform configuration (Figure 13). Occasional mitoses are seen but are not abundant. Atypical forms are usually not seen. The tumor may extend to the epidermis or, alternatively, a grenz zone is seen. Lateral extension of the tumor beyond the dermal component may be marked but subtle. DFSP has a characteristic pattern of subcutaneous infiltration, including growth along septa and between lipocytes in a honeycomb configuration or horizontally layered, parallel to the epidermal surface. Other findings in DSFP are seen rarely, including multinucleated giant cells, hypercellular zones, and myoid or myofibroblastic differentiation [26-28]. Occasional tumors contain myxoid areas, and when prominent, the storiform pattern becomes less apparent. Unusual variants include sclerosing [29, 30] and pigmented types. Histology with a discrete fascicular or “herringbone” pattern may suggest fibrosarcomatous transformation. The mitotic rate is usually, but not always, higher when this occurs, although occasional examples of DFSP demonstrate up to 35 mitotic figures per high power field [31]. It is currently unclear whether fibrosarcomatous areas are more common in recurrent lesions. Recent studies have shown this not to be the case.

The tumor cells in DSFP stain immunohistochemically with CD34 (Figure 14), the human progenitor cell antigen, in a significant proportion of its cells, making CD34 a highly sensitive marker for this entity. Care should be taken not to interpret entrapped CD34+ dermal dendritic cells as tumor cells.

Almost all cases of DFSP express the chromosomal translocation t(17:22) when investigated with the newest molecular techniques, including multiplex reverse transcription polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) [32]. The translocation results in a fusion of the collagen type Iα1 (COL1A1) gene on chromosome 17 with the platelet-derived growth factor beta (PDGFβ) on chromosome 22 and is most commonly located on a ring chromosome. The fusion transcript leads to constitutive activation of the PFGRβ protein tyrosine kinase, resulting in uncontrolled tumor growth. DFSP has been found to differ from other soft tissue tumors with similar histology by the expression of this distinct set of genes. In addition, PDGFRβ, the receptor for PDGFβ, is highly expressed in DFSP, suggesting an autocrine stimulatory loop that may contribute to tumorigenesis [33].
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PROGNOSIS AND TREATMENT.
While generally indolent, the tumor possesses a tendency for progressive growth, recurrence, and rarely distant metastasis. With wide excision and careful pathologic examination of surgical margins, even local recurrence is extremely low [34]. In one large study of 218 DFSP patients, there was no significant difference in crude cumulative incidence of local relapses between primary and recurrent disease and in cases with positive and negative margins [35].

Fibrosarcomatous or malignant fibrous histiocytomatous transformation can occur, although the effect on the biologic behavior of such a transformation is controversial. Adequacy of wide excision may be more important to prognosis than the presence of the sarcomatous component per se [36-40]. Transformation to a fibrosarcomatous component has been associated with microsatellite instability [41] and p53 mutations [41, 42].

CUTANEOUS LEIOMYOSARCOMA.
CLINICAL FEATURES
Primary leiomyosarcomas (LMS) of the skin are relatively rare sarcomas, reported infrequently in the literature. LMS of the skin are divided into dermal and subcutaneous types. The dermal type is discussed here and tends to develop in adults of middle to older age. It arises as one or several dermal or subcutaneous nodules, most often on the hip, thigh, or knee [43]. Other locations, including the face and scrotum, are reported[44]. Many tumors are present for years before coming to clinical attention [45] and often resemble epidermal cysts. Women may be slightly more affected than men. Lesions can be painful.

HISTOPATHOLOGY (FIGURES 15, 16, 17)
Intra-dermal LMS is usually poorly circumscribed, in contrast with nodular lesions within the subcutis. It is composed of interwoven fascicles of spindled cells which merge with a collagenous stroma. Subcutaneous involvement is sometimes present. Histopathologically, two growth patterns were described by Kaddu et al [46]: nodular and diffuse. Intra-dermal LMS with a nodular growth pattern showed high cellularity, prominent nuclear atypia, numerous mitoses, and sometimes extensive necrosis. Intra-dermal LMS with a diffuse growth pattern, on the other hand, revealed low cellularity, well-differentiated smooth muscle cells, few mitotic figures, and few or no necrotic cells, making the diagnosis of a malignant neoplasm difficult. Unusual variants are described, including a desmoplastic type, which can be misdiagnosed as cutaneous sclerosis [39, 47-50].

Immunohistochemical staining generally shows positivity for vimentin and smooth muscle actin (Figure 17), regardless of tumor site [44, 51]. Desmin[46], cathepsin B, and myelin basic protein positivity is variable. Dermal tumors are more likely than subcutaneous tumors to express S-100 protein [52]. Interestingly, cytokeratin positivity is occasionally seen [46]. In addition, positivity for p53 protein is seen in some cases, suggesting the involvement of this tumor suppressor gene in the pathogenesis [51].
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PROGNOSIS AND TREATMENT

In a series of 65 primary cutaneous LMS reported by Fields et al. and in smaller series reported by other authors [46, 48], LMS can recur, sometimes due to incomplete surgical excision [51]. None metastasize, despite high mitotic activity and marked cytologic atypia [53] in some cases. Recurrent tumors may be more atypical and located deeply [51]. Reported cases of metastases appear in the older literature [54].

SUMMARY

Spindle cell malignancies of the skin, some of which are not particularly common, are nevertheless seen by the practicing dermatologists and pathologists. Such tumors are not always easily differentiated on histologic findings alone and many, if not all, must be confirmed with immunohistochemical staining (Table 1). A thorough familiarity with these lesions is a necessity, as prognosis and treatment may be different.

Table 1. Immunohistochemical Staining in Spindle Cell Malignancies of the Skin

<table>
<thead>
<tr>
<th>Stain</th>
<th>DM</th>
<th>AFX</th>
<th>LMS</th>
<th>DPSP</th>
<th>SICC</th>
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<tr>
<td>SMA</td>
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SMA, smooth muscle actin; DM, desmoplakin; AFX, affixin; LMS, leiomyosarcoma; DPSP, dermatofibrosarcoma protubersans; SICC, spindle cell squamous cell carcinoma.
References

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