Cutaneous Spindle Cell Neoplasms
Pattern-Based Diagnostic Approach

Joon Hyuk Choi, MD, PhD; Jae Y. Ro, MD, PhD

Context.—Spindle cell neoplasms arising in the skin comprise a heterogeneous group of tumors with divergent lineages. Cutaneous spindle cell neoplasms are relatively common and present surgical pathologists with diagnostic challenges. Recognition of their histopathologies is important for correct diagnosis and management. The current review presents a pattern-based diagnostic approach to common cutaneous spindle cell neoplasms that often cause diagnostic difficulties.

Objective.—To provide a useful guide for diagnosis of cutaneous spindle cell neoplasms.

Data Sources.—PubMed (US National Library of Medicine) reports and the authors’ personal experiences are reviewed.

Conclusions.—The authors briefly summarize the histologic features and differential diagnoses of common cutaneous spindle cell neoplasms.

Cutaneous neoplasms entirely or predominantly composed of spindle cells constitute a heterogeneous group of mesenchymal and nonmesenchymal tumors. Cutaneous spindle cell neoplasms are often diagnostically challenging because of considerable morphologic overlap among the various tumor types that compose this group. Furthermore, they are often difficult to diagnose accurately, especially when only partial or superficial samples are available. However, a pattern-based diagnostic approach can help pathologists arrive at a specific diagnosis or differential diagnoses of tumors and tumorlike lesions. Here, we review the histologic features and differential diagnoses of common cutaneous spindle cell neoplasms, based on their architectural (growth) patterns.

DIAGNOSTIC APPROACH TO CUTANEOUS SPINDLE CELL NEOPLASMS

Cutaneous spindle cell lesions encompass a heterogeneous group of tumors that range from reactive to benign, borderline, and malignant tumors. The approach used for the diagnosis of these tumors should be based on knowledge of the relative frequencies of different tumor types, appropriate consideration of clinical context, and correct interpretation of histologic features. Benign lesions are more common than malignant tumors. Fibrous histiocytoma (FH; also known as dermatofibroma) is one of the most common cutaneous mesenchymal neoplasms. Cutaneous soft tissue sarcomas represent less than 1% of malignant tumors. The common primary cutaneous sarcomas include dermatofibrosarcoma protubersans (DFSP), leiomyosarcoma, and pleomorphic dermal sarcoma (PDS) (also known as an aggressive variant of atypical fibroxanthoma [AFX]). Common vascular neoplasms include Kaposi sarcoma (KS) and angiosarcoma.1-3 Kaposi sarcoma is among the most common cutaneous soft tissue sarcomas in the United States.4

Before interpreting the biopsy, pathologists need to know (1) patient age and sex, (2) tumor size and duration, and (3) tumor location and depth. The first and important step in the diagnostic approach involves careful microscopic examination of hematoxylin and eosin-stained sections. It is important that the following histologic features be evaluated: (1) architectural (growth) pattern of the tumor, (2) overall cellularity, (3) appearance of cells, (4) amount and type of matrix formation, (5) tumor and adjacent tissue interfaces, (6) vascularity, (7) tumor necrosis, and (8) mitotic activity.

At low power, the preservation of normal architecture, zonation, lesional symmetry, and overall cellularity aid differentiation between benign and malignant tumors. At high-power magnification, atypical mitoses and nuclear atypia are more often associated with malignancy. In terms of practical diagnostic approaches, the pattern-based approach substantially aids the diagnostic process. Although not all architectural patterns permit a definite diagnosis, they facilitate the narrowing of differential diagnostic possibilities. A list of architectural patterns of cutaneous spindle cell neoplasms is provided in Table 1.

The important diagnostic issues include (1) distinguishing spindle cell squamous cell carcinoma and malignant...
Cutaneous Spindle Cell Neoplasms

Advances have recently been made in the identification of underlying genetic alterations in cutaneous soft tissue tumors.7 The definition of unique pathologic entities has increased our understanding of the biological mechanisms responsible for tumor development and progression. Recently identified genetic alterations in cutaneous mesenchymal neoplasms are summarized in Table 3.8–19 It is evident that molecular testing has acquired an increasingly important role in the diagnosis of soft tissue neoplasms.

Strict diagnostic criteria should always be applied, but it may not be possible to classify a subset of spindle cell lesions with certainty. In this case, clinicopathologic correlation and good communication with the clinician are important. A descriptive diagnosis that conveys all available information (eg, status of excision margins, presence of aggressive features, and probable line of differentiation) is usually very helpful clinically and aids appropriate patient management.5

FASCICULAR PATTERN

Intradermal Nodular Fasciitis

Nodular fasciitis is a benign, self-limiting fibrous neoplasm with a predilection for the upper extremities, trunk, and head and neck. It occurs in all age groups but more often in young adults. Although it usually arises within subcutaneous tissues, it may also occur rarely in the dermis.20,21 Nodular fasciitis usually presents as a solitary, painless, rapidly growing nodule that usually grows in less than 3 months. Intradermal nodular fasciitis is not widely recognized to arise within dermis, and thus may cause diagnostic confusion in this uncommon setting.

Grossly, lesions are yellow-white, solid, nodular, rubbery, and lobulated. Histologically, the lesions are well circumscribed but not encapsulated. Overall cellularity varies widely. Lesions may be hypercellular and composed of bland, uniform spindle cells, with a fascicular or tissue-culture–like growth pattern (Figure 1, A and B). Stromal collagen is variably loose myxoid, focally microcystic, to collagenous. Extravasated erythrocytes, lymphocytes, plasma cells, and mast cells are frequently present. Immunohistochemically, the cells are often diffusely positive for SMA and negative for cytokeratins, S100 protein, and CD34.

The differential diagnosis of intradermal nodular fasciitis includes FH and spindle cell sarcomas. Fibrous histiocytoma is composed of spindle to histiocytic cells with entrapped hyaline collagen bundles at the peripheries of the lesion. Overlying epidermis often shows acanthosis. Nodular fasciitis is often mistaken for a sarcoma when biopsy shows high cellularity and frequent mitotic activity. However, in contrast to sarcomas, nodular fasciitis grows rapidly, is relatively small, and lacks nuclear hyperchromasia, pleomorphism, and atypical mitoses.

Acral Fibromyxoma

Acral fibromyxoma (digital fibromyxoma) is a benign dermal fibroblastic neoplasm of acral sites. Fetsch et al22 first

<table>
<thead>
<tr>
<th>Table 1. Architectural Patterns of Cutaneous Spindle Cell Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fascicular pattern</td>
</tr>
<tr>
<td>Intradermal nodular fascitis</td>
</tr>
<tr>
<td>Acral fibromyxoma</td>
</tr>
<tr>
<td>Pilar leiomyoma</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Atypical fibroxanthoma</td>
</tr>
<tr>
<td>Storiform/whorled pattern</td>
</tr>
<tr>
<td>Fibrous histiocytoma (dermatofibroma)</td>
</tr>
<tr>
<td>Soft tissue perineurioma</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
</tr>
<tr>
<td>Lobulated/plexiform pattern</td>
</tr>
<tr>
<td>Dermal nerve sheath myxoma</td>
</tr>
<tr>
<td>Cellular neurothekeoma</td>
</tr>
<tr>
<td>Plexiform schwannoma</td>
</tr>
<tr>
<td>Biphasic pattern</td>
</tr>
<tr>
<td>Myofibroma/myopericytoma</td>
</tr>
<tr>
<td>Nonmesenchymal neoplasms mimicking cutaneous spindle cell</td>
</tr>
<tr>
<td>mesenchymal tumors</td>
</tr>
<tr>
<td>Spindle cell squamous cell carcinoma</td>
</tr>
<tr>
<td>Desmoplastic melanoma</td>
</tr>
</tbody>
</table>

**Table 2. Immunohistochemistry of Selected Cutaneous Spindle Cell Neoplasms**

<table>
<thead>
<tr>
<th></th>
<th>Leiomyosarcoma</th>
<th>Angiosarcoma</th>
<th>Atypical Fibroxanthoma</th>
<th>Spindle Cell SCC</th>
<th>Desmoplastic Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td>+</td>
<td>–</td>
<td>+/–</td>
<td>+/–</td>
<td>–</td>
</tr>
<tr>
<td>Desmin</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+/–</td>
</tr>
<tr>
<td>CD34</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>S100 protein</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Endothelial markers (eg, CD31, ERG)</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Melanocytic markers (eg, HMB-45, Melan-A)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+/–</td>
<td>–</td>
</tr>
<tr>
<td>Epithelial markers (eg, CK [AE1/AE3], EMA)</td>
<td>+/–</td>
<td>+/–</td>
<td>–</td>
<td>+/–</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: CK, cytokeratin; EMA, epithelial membrane antigen; SCC, squamous cell carcinoma; SMA, smooth muscle actin; +, positive; +/–, variable; –, negative.
described it as superficial acral fibromyxoma. Acral fibromyxoma is usually encountered in middle-aged adults, but can affect any age group, and exhibits male predominance. The lesions typically present as solitary, slowly growing subungual or periungual masses in the finger or toe (Figure 2, A). Tumors range in size from less than 1 cm to 2 cm. Grossly, lesions are well marginated. Microscopically, lesions are low to moderately cellular, and consist of bland spindle or stellate-shaped cells in a myxoid to collagenous matrix (Figure 2, B). The tumor cells are arranged randomly or in a loose fascicular pattern, with a mildly attenuated vasculature. Multinucleated stromal cells are occasionally present. Nuclear atypia is generally minimal to absent. Mitotic figures are rare. Mast cells are commonly present. Immunohistochemically, most cases are positive for CD34, and occasionally show focal reactivity for SMA and EMA. The differential diagnosis of acral fibromyxoma includes superficial angiomyxoma, perineurioma, and myxoid neurofibroma. Superficial angiomyxoma shows a predilection for head and neck rather than acral sites and shows a lobular growth pattern; prominent thin-walled, arborizing vessels; and neutrophil infiltration. In regard to its differential diagnosis, perineurioma can overlap with acral fibromyxoma morphologically and immunohistochemically. Perineurioma shows a whorled growth pattern and bipolar cytologic process. Myxoid neurofibroma can be excluded when S100 protein is not expressed.

**Pilar Leiomyoma**

Benign dermal smooth muscle neoplasms may be classified in pilar and genital types. Pilar leiomyoma arises from arrector pili, whereas genital leiomyoma arises from genital smooth muscle. Pilar leiomyoma may be solitary or multiple. Hereditary leiomyomatosis and renal cell cancer syndrome is an autosomal dominant disorder caused by heterozygotic germline mutations in the fumarate hydratase (FH) gene, and is characterized by predisposition to cutaneous and uterine leiomyomatosis. Pilar leiomyoma usually affects adolescents or young adults, and the lesions commonly occur on extensor surfaces of extremities, trunk, and head and neck. It forms small, pink to brown, painful papules or nodules, which are usually less than 2 cm in size (Figure 3, A).

Histologically, pilar leiomyoma is an ill-defined, intradermal lesion and composed of intersecting fascicles of well-differentiated smooth muscle cells (Figure 3, B). The cells have blunt-ended, cigar-shaped nuclei and brightly eosinophilic cytoplasm. Mitotic figures are only rarely seen. Tumor nuclei with large orangophilic nucleoli surrounded by a perinucleolar halo similar to the changes found in hereditary leiomyomatosis and renal cell cancer may be seen. Immunohistochemically, the tumor cells are positive for SMA and desmin. Leiomyomas in hereditary leiomyomatosis and renal cell cancer syndrome are often immunohistochemically negative for fumarate hydratase.

The differential diagnosis of pilar leiomyoma includes smooth muscle hamartoma, dermatomyofibroma, and cutaneous leiomyosarcoma. Smooth muscle hamartoma is characterized by a haphazard arrangement of smooth muscle bundles separated by abundant dermal collagen. Dermatomyofibroma is solitary and composed of spindled myofibroblasts arranged in parallel to epidermis and usually negative for desmin. Cutaneous leiomyosarcoma shows more nuclear atypia and mitotic activity.

**Leiomyosarcoma**

Leiomyosarcoma is a malignant neoplasm composed of cells showing smooth muscle differentiation. Primary cutaneous leiomyosarcoma accounts for a significant proportion of superficial soft tissue sarcomas, but it is more common in deep locations, such as the retroperitoneum and abdomen. It arises in the extremities, trunk, and head and neck. It often occurs in middle-aged and elderly adults, with male predominance. Cutaneous leiomyosarcoma is very rare in children.

Histologically, cutaneous leiomyosarcoma has an infiltrative growth pattern, and consists of atypical spindle tumor cells arranged in a fascicular growth pattern. The tumor cells have elongated, blunt-ended nuclei with brightly eosinophilic cytoplasm (Figure 4, A and B). Nuclear atypia and mitoses are present. Immunohistochemically, the tumor cells are positive for SMA, desmin, and h-caldesmon. When the tumors formerly known as cutaneous leiomyosarcomas are confined to the dermis or show only minimal subcutaneous involvement, they may recur locally but do not seem to metastasize. The term atypical intradermal smooth muscle tumor has been connected with better prognosis in contrast to its deeper counterparts. Recently, Aneiros-Fernandez et al found that primary cutaneous leiomyosarcomas have risk of metastasizing. Also, in certain cases, they have been the cause of death; thus, the authors recommend that the term atypical intradermal smooth muscle tumor should be avoided. Because of possible

### Table 3. Recently Identified Genetic Alterations in Cutaneous Mesenchymal Neoplasms

<table>
<thead>
<tr>
<th>Genetic Aberrations</th>
<th>Fusion Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous histiocytoma (dermatofibroma)</td>
<td>PRKC gene fusion</td>
</tr>
<tr>
<td>Epithelioid fibrous histiocytoma</td>
<td>ALK gene rearrangement</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>t(17;22)(q21;q13)</td>
</tr>
<tr>
<td>Infantile myofibromatosis</td>
<td>PDGFRB gene mutation</td>
</tr>
<tr>
<td>Myopericytoma</td>
<td>PDGFRB gene mutation</td>
</tr>
<tr>
<td>Spindle cell hemangioma</td>
<td>IDH1 gene mutation</td>
</tr>
<tr>
<td>Epithelioid hemangioma</td>
<td>FOS gene rearrangement</td>
</tr>
<tr>
<td>Epithelioid hemangioendothelioma</td>
<td>t(1;3)(p36;q25)</td>
</tr>
<tr>
<td>Pseudomyogenic hemangioendothelioma</td>
<td>t(7;19)(q22;q13)</td>
</tr>
<tr>
<td>Cutaneous angiosarcoma</td>
<td>MYC gene amplification</td>
</tr>
<tr>
<td>Cutaneous syncytial myoepithelioma</td>
<td>EWSR1 gene rearrangement</td>
</tr>
<tr>
<td>Hemosiderotic fibrolipomatous tumor</td>
<td>t(1;10)(p22;q24)</td>
</tr>
<tr>
<td>Epithelioid hemangioma14</td>
<td>PDGFRB, CD63-PRKCD, LAMTOR1-PRKCD</td>
</tr>
<tr>
<td>Hemosiderotic fibrolipomatous tumor19</td>
<td>PDPN-PRKCB, CD63-PRKCD, LAMTOR1-PRKCD</td>
</tr>
<tr>
<td>Hemangiopericytoma18</td>
<td>COL1A1-PDGFRB</td>
</tr>
<tr>
<td>Dermal lobular capillary hemangioma17</td>
<td>WWTR1-FOSB</td>
</tr>
<tr>
<td>Cutaneous angiosarcoma11</td>
<td>WWTR1-CAMTA1, YAP1-TFE3</td>
</tr>
<tr>
<td>Cutaneous angiosarcoma12</td>
<td>SERpine1-FOSB</td>
</tr>
<tr>
<td>Hemangiopericytoma10</td>
<td>TGFBR3-MGEA5</td>
</tr>
</tbody>
</table>
Figure 1. Intradermal nodular fasciitis. A, Low-power view shows an ill-defined lesion arising in the dermis. B, The lesion shows uniform spindle cells with tapering nuclei, with a fascicular pattern (hematoxylin-eosin, original magnifications ×4 [A] and ×100 [B]).

Figure 2. Acral fibromyxoma. A, Dome-shaped, subungual mass is present on the left fifth toe. B, Bland spindle cells are arranged in a random or loosely fascicular pattern within fibromyxoid stroma (hematoxylin-eosin, original magnification ×100).

Figure 3. Pilar leiomyoma. A, Multiple small pink to brown papules are present on the left upper arm. B, The lesions are composed of bundles or fascicles of smooth muscle cells mimicking arrector pili muscles (hematoxylin-eosin, original magnification ×100).
Figure 4. Cutaneous leiomyosarcoma. A, Scanning magnification shows an ill-defined, infiltrative tumor in the dermis, with superficial subcutaneous extension. B, The tumor cells have elongated, blunt-ended nuclei and brightly eosinophilic cytoplasm, and are arranged in a fascicular pattern. Nuclear atypia and frequent mitoses are present (hematoxylin-eosin, original magnifications ×1 [A] and ×200 [B]).

Figure 5. Kaposi sarcoma. A, The tumor is composed of cellular, uniform spindle cells arranged in a fascicular pattern. Intervening slitlike or sievelike spaces contain erythrocytes. Intracytoplasmic hyaline globules (arrow) are present. B, The tumor cells show nuclear staining for human herpesvirus 8 (hematoxylin-eosin, original magnification ×200 [A]; original magnification ×200 [B]).

Figure 6. Angiosarcoma. A, Poorly differentiated angiosarcoma shows spindle tumor cells with solid and fascicular growth patterns. Anastomosing vascular channels are focally observed. B, The tumor cells are diffusely positive for CD31 (hematoxylin-eosin, original magnification ×200 [A]; original magnification ×200 [B]).
metastasis, it is advisable to monitor these lesions for more than 5 years.

The differential diagnosis of cutaneous leiomyosarcoma includes cutaneous FH, pseudomyogenic hemangioendothelioma, and spindle cell squamous cell carcinoma. Cutaneous cellular FH lacks blunt-ended nuclei, nuclear atypia, and bright eosinophilic cytoplasm. Pseudomyogenic hemangioendothelioma shows loose fascicles and sheets of plump spindle cells with vesicular nuclei and abundant eosinophilic cytoplasm and is positive for cytokeratins, ERG, and CD31. Spindle cell squamous cell carcinoma is positive for cytokeratin and can be focally positive for SMA, but is negative for desmin and h-caldesmon.

Kaposi Sarcoma

Kaposi sarcoma is a locally aggressive endothelial tumor or a tumorlike lesion that usually presents with cutaneous lesions in the form of patches, plaques, or nodules. The 4 clinicopathologic types of KS are (1) classic indolent KS, (2) endemic African KS, (3) iatrogenic KS, and (4) AIDS-associated KS. All forms are associated with human herpesvirus 8 (HHV-8) infection. Skin lesions range in size from small to several centimeters. The classic type of KS is characterized by purplish-reddish blue to dark brown macules, plaques, and nodules.

Histologically, in the plaque stage, the number of irregularly jagged vascular channels is increased in the reticular dermis. In the plaque stage, more extensive vascular proliferation with spindle cell infiltration is present. Nodular KS shows a well-circumscribed, cellular dermal nodule composed of spindle cells arranged in an intersecting fascicular pattern (Figure 5, A). In addition, there are slitlike or sievelike spaces containing erythrocytes, intracytoplasmic hyaline globules, and lymphoplasmacytic infiltrate. Immunohistochemically, the tumor cells are positive for CD31, CD34, ERG, FLI-1, and podoplanin (D2-40). Notably, the nuclear expression for HHV-8 (latent nuclear antigen 1) is highly sensitive and specific for KS (Figure 5, B).

The differential diagnosis of nodular KS includes leiomyosarcoma, spindle cell squamous cell carcinoma, and malignant melanoma. Leiomysarcoma, spindle cell squamous cell carcinoma, and malignant melanoma can be excluded based on histologic features and negativity for endothelial markers. Immunohistochemistry for HHV-8 is extremely useful for diagnosis, as other spindle cell vascular tumors are nearly always negative for HHV-8 (Figure 5, B).

Angiosarcoma

Angiosarcoma is a rare malignant vascular neoplasm that recapitulates the morphologic and functional features of endothelial cells. In a superficial location, angiosarcoma occurs in 3 distinct clinical settings: (1) the sun-exposed skin of face and scalp in the elderly, (2) the extremities of patients with chronic lymphedema, and (3) at sites previously exposed to radiation therapy. Pediatric cutaneous angiosarcomas are rare, and differ from those in adults in terms of their clinical presentation and associated conditions.

Histologically, angiosarcoma displays a broad morphologic spectrum ranging from areas of well-formed anastomosing vessels lined by mildly atypical endothelial cells to solid sheets of high-grade epithelioid spindle cells. Angiosarcomas are composed of spindle cells with solid or fascicular growth patterns (Figure 6, A). The presence of vasoformative channels, intracytoplasmic vacuoles, and marked stromal hemorrhage are helpful diagnostic clues. The tumor cells express endothelial markers such as CD31, CD34 (Figure 6, B), ERG, and FLI-1. Cytokeratins may also be expressed, especially in epithelioid angiosarcoma.

The differential diagnosis of spindle cell angiosarcoma includes KS, spindle cell squamous cell carcinoma, and spindle cell melanoma. Immunohistochemical analysis aids its differential diagnosis. Angiosarcoma is negative for HHV-8. Spindle cell squamous cell carcinoma shows more nuclear pleomorphism and strong and diffuse positivity for epithelial markers. Spindle cell melanoma is distinguished from angiosarcoma by positivity for melanocytic markers.

Atypical Fibroxanthoma

Atypical fibroxanthoma is a rare, benign, dermally based tumor of uncertain lineage. Atypical fibroxanthoma occurs almost exclusively in sun-damaged skin of elderly patients.

Figure 7. Atypical fibroxanthoma, spindle cell variant. A, Scanning magnification shows a well-marginated, exophytic tumor confined to the dermis. Ulceration and lateral collarette of the epidermis are present. B, The tumor is composed of spindle tumor cells arranged in a fascicular pattern (hematoxylin-eosin, original magnifications ×2 [A] and ×200 [B]).
Figure 8. Fibrous histiocytoma (FH) and variants. A, Conventional FH. Scanning magnification shows a dermally based lesion. B, Conventional FH. The lesion is composed of bland spindle cells arranged in a storiform pattern. Hyalinized collagen bundles are also present. C, Cellular FH. Scanning magnification shows a dermal mass with extension into the subcutaneous tissue. D, Cellular FH. The mass is composed of highly cellular, uniform spindle cells arranged in a storiform pattern. E, Aneurysmal FH. Grossly, the lesion is poorly demarcated, brownish and hemorrhagic. F, Aneurysmal FH. The lesion shows blood-filled spaces, hemosiderin deposition, and histiocytoid cells. G, Atypical FH. The tumor shows moderately atypical cells...
especially in the head and neck area. Therapeutic irradiation and immunosuppression may play additional pathogenetic roles. The tumors grow slowly and are pinkish red or flesh colored and usually less than 2 cm in diameter. Atypical fibroxanthoma has a good prognosis following complete excision.

Histologically, AFX presents a well-demarcated, nodular exophytic growth. It is confined to the dermis and lacks necrosis and infiltrative growth; the epidermis frequently shows ulceration and collarette formation (Figure 7, A). The morphologic spectrum of AFX is broad, and several histologic variants have been described. The spindle cell variant is composed of atypical monomorphic spindle cells arranged in an intersecting fascicular pattern (Figure 7, B). Frequent mitoses, including abnormal forms, are seen. There are no diagnostic immunohistochemical makers for AFX; however, nonspecific positive stainings for CD10, SMA, CD68, and CD99 are often present.

Atypical fibroxanthoma is a diagnosis of exclusion. Its differential diagnosis includes spindle cell squamous cell carcinoma, spindle cell melanoma, and PDS. In spindle cell squamous cell carcinoma, squamous differentiation and cytokeratin expression are present. Spindle cell melanoma is positive for S100 protein, whereas AFX is entirely negative. In contrast to AFX, PDS is an ill-defined, infiltrative malignant neoplasm that invades deep subcutaneous tissue and shows tumor necrosis and lymphovascular invasion with local recurrence in 28% and metastasis in 10%. In a recent genetic study, AFX and PDS were found to be related, and it was suggested that they potentially represent 2 ends of a common tumor type.

STORIFORM/WHORLED PATTERN

Fibrous Histiocytoma (Dermatofibroma)

Fibrous histiocytoma is a common benign dermal mesenchymal tumor characterized histologically by the proliferation of mononuclear, spindle to round or histiocytic cells. Fibrous histiocytoma may develop at any age, but it usually presents during the third and fourth decades. Typically, it occurs on the extremities and trunk and forms a small, dome-shaped elevation that is sometimes pigmented and rarely multiple. Cutaneous FH may rarely metastasize to lung, lymph node, or soft tissue. Although most FHs are dermally based, deep benign FH arises in subcutaneous or deep soft tissue and has a higher recurrence rate than conventional FH.

Cutaneous FH presents as an ill-defined dermal lesion associated with hyperplasia of overlying epidermis. Histologically, the lesion is composed of short spindle and ovoid cells with slightly irregularly shaped nuclei arranged in a storiform fascicular pattern (Figure 8, A and B). There is a variable admixture of inflammatory cells, foamy macrophages, Touton giant cells, and siderophages. Entrapped thickened, hyaline collagen bundles are seen at the peripheries of the lesion. Furthermore, hyperplasia of overlying epidermis is present. Immunohistochemically, the tumor cells are often positive for factor XIIIa, SMA, and CD68, and desmin and CD34 are often expressed.

Fibrous histiocytoma has multiple variants, and many cases exhibit overlapping features of more than one subtype. Furthermore, the recognition of these subtypes is important to achieve accurate diagnosis. The cellular FH variant is characterized by highly cellular spindle cells arranged in a fascicular pattern with increased mitotic activity (Figure 8, C and D). Aneurysmal FH shows blood-filled cystic spaces and marked hemosiderin deposition (Figure 8, E and F). Epithelioid FH presents a polypoid growth composed of epithelioid cells with vesicular nuclei and abundant eosinophilic cytoplasm. In addition, the presence of ALK gene rearrangement and ALK overexpression in epithelioid FH suggests that epithelioid FH is a biologically distinct tumor type, unrelated to conventional FH and histologic variants. This tumor is another example to express ALK overexpression besides the well-known inflammatory myofibroblastic tumor. Atypical FH displays marked nuclear pleomorphism and hyperchromasia and atypical mitosis (Figure 8, G and H).

The differential diagnosis of FH includes DFSP and leiomyosarcoma. Dermatofibrosarcoma protubersans shows honeycomb infiltration of subcutis and CD34 expression. Leiomyosarcoma has blunt-ended, parallel-sided nuclei, more eosinophilic cytoplasm, and desmin and h-caldesmon expression. Aneurysmal FH is distinguished from angiomatoid FH by its deep location, fibrous and lymphoid cuff at the periphery, and desmin expression. Atypical FH is distinguished from AFX and superficial pleomorphic sarcomas by its appearance in extremities, epidermal hyperplasia, and the presence of conventional FH features.

Perineurioma

Perineurioma is a rare benign tumor that is composed entirely of perineurial cells. Two main forms exist: intraneural and extraneural. Extraneural perineuriomas are subclassified as soft tissue, sclerosing, and reticular subtypes. Perineurioma arises mainly in the skin or soft tissue, commonly in extremities, trunk, or head and neck, and usually affects male or female adults. Tumor sizes range from 0.3 to 20 cm (mean, 4.1 cm).

Histologically, perineurioma is composed of bland ovoid to spindle cells with elongated slender nuclei and long, bipolar cytoplasmic processes (Figure 9, A). The tumor cells are arranged in a storiform, lamellar, or perivascular whorled pattern. The stroma is collagenous or focally myxoid. Recently, hybrid schwannoma/perineurioma with features of schwannoma and perineurioma tumors was described. Immunohistochemically, the tumor cells are positive for perineurial markers such as EMA (Figure 9, B) claudin-1, and GLUT1. CD34 is also positive (Figure 9, C) in about two-thirds of cases.

The differential diagnosis of perineurioma includes neurofibroma, DFSP, cutaneous meningioma, and low-grade fibromyxoid sarcoma. Neurofibroma is positive for S100 protein. Dermatofibrosarcoma protubersans can resemble perineurioma, particularly in a superficial biopsy, and is negative for EMA. Cutaneous meningioma typically occurs on scalps of infants and children, and is negative for CD34. Some perineuriomas can resemble low-grade fibromyxoid sarcoma, which is positive for MUC4.

with large nuclei and abundant cytoplasm. H, Atypical FH. Uniform spindle cells and focally atypical larger cells are arranged in a storiform pattern in different areas of the same tumor. This appearance is reminiscent of conventional FH (hematoxylin-eosin, original magnifications ×2 [A and C], ×200 [B and G], and ×100 [D, F, and H]).

Arch Pathol Lab Med—Vol 142, August 2018
Cutaneous Spindle Cell Neoplasms—Choi & Ro
Figure 9. Perineurioma. A, Bland spindle cells are arranged in a storiform or whorled pattern within collagenous and myxoid stroma. These cells have elongated nuclei with tapering ends and long, thin cytoplasmic processes. B, The tumor cells show epithelial membrane antigen (EMA) expression highlighting cytoplasmic process. C, The tumor cells show CD34 expression (hematoxylin-eosin, original magnification ×200 [A]; original magnification ×200 [B and C]).

Figure 10. Dermatofibrosarcoma protuberans (DFSP) and variants. A, Conventional DFSP. Cellular, uniform spindle cells are arranged in a storiform pattern. B, Conventional DFSP. The tumor cells infiltrate subcutaneous fat tissue in a honeycomb pattern. C, Pigmented DFSP (Bednar tumor). Melanin pigment-containing cells are present. D, Fibrosarcomatous DFSP. Fibrosarcomatous transformation showing increased cellularity, fascicular pattern, and frequent mitosis is present. E, CD34 expression is lost (hematoxylin-eosin, original magnifications ×100 [A, B, and D] and ×200 [C]; original magnification ×100 [E]).
Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a superficial, low-grade, locally aggressive fibroblastic neoplasm. It is relatively common and is more frequent in males. It occurs most frequently between the ages of 25 and 45 years, but some cases also occur in childhood or arise congenitally. Most lesions occur in the trunk and the proximal extremities. The tumor begins as a dermal plaque or nodule and grows slowly, sometimes becoming multinodular. Dermatofibrosarcoma protuberans is notable for its high recurrence after surgical resection, but has a low metastatic potential.52

Histologically, DFSP is composed of uniform spindle tumor cells with minimal cytology and an indistinct margin. Its tumor cells exhibit a monotonous, storiform growth pattern and extend into subcutaneous fat with a characteristic honeycomb appearance (Figure 10, A and B). There are several variants of DFSP.53 Pigmented DFSP (Bednar tumor) has melanin-containing cells present singly or in small clusters (Figure 10, C). Myxoid DFSP is characterized by evenly spaced, bland spindle cells with oval to stellate nuclei, abundant myxoid stroma, thin-walled vessels throughout the stroma, and a honeycomb pattern.54 In 10% to 15% of cases, fibrosarcomatous DFSP arises de novo or more rarely exhibits local recurrences.55 The fibrosarcomatous component is characterized by greater cellularity, more atypia, increased mitotic activity (>5/10 high-power fields), and a fascicular architecture (Figure 10, D). Immunohistochemically, DFSP shows diffuse CD34 expression, which is reduced or lost in regions of fibrosarcomatous changes (Figure 10, E).

The differential diagnosis of conventional DFSP includes cellular FH and perineurioma. Cellular FH lacks the monotonous appearance, honeycomb-like fat infiltration, and diffuse CD34 expression of DFSP. Perineurioma does not show infiltrative growth and is positive for EMA. Differential diagnosis of myxoid DFSP is diverse and the lesion may be easily confused with a few myxoid neoplasms, such as myxoid neurofibroma, superficial angiomyxoid, myxoid liposarcoma, and low-grade myxofibrosarcoma. Recognition of the typical histologic features of myxoid DFSP is required for a correct diagnosis.

LOBULATED/PLEXIFORM PATTERN

Dermal Nerve Sheath Myxoma

Dermal nerve sheath myxoma is a rare benign peripheral nerve sheath tumor that exhibits Schwann cell differentiation. It mainly affects young and middle-aged adults, with approximately equal frequencies in males and females. Dermal nerve sheath myxoma occurs in the extremities, especially in the hands and fingers, followed by the knees, lower legs, ankles, feet, and head and neck.56 Patients typically present with superficial, slowly growing masses. Tumors range from 0.4 to 4.5 cm in the greatest dimension, and have a high rate of local recurrence when incompletely excised.

Histologically, dermal nerve sheath myxoma shows a characteristic lobulated growth pattern with sharply demarcated lobules separated by fibrous tissue (Figure 11, A). Lobules contain abundant myxoid matrix and tumor cells, which are spindle, epithelioid, ringlike, or stellate shaped and arranged in cords, nests, or syncytial-like aggregates (Figure 11, B). Mitotic figures are uncommon. Immunohistochemically, the tumor cells are positive for S100 protein (Figure 11, C) and GFAP, and EMA-positive perineurial cells are often seen at the peripheries of tumor lobules.

The differential diagnosis of dermal nerve sheath myxoma includes acral fibromyxoma, superficial angiomyxoid, soft tissue myoepithelioma, and cellular neurothekeoma. Acral fibromyxoma has a less myxoid matrix than dermal nerve sheath tumor and is negative for S100 protein. Superficial angiomyxoid lacks a peripheral fibrous circumscription and contains thin-walled blood vessels and infiltrating neutrophils. Soft tissue myoepithelioma lacks the sharply demarcated lobules of dermal nerve sheath myxoma, and is positive for cytokeratins and EMA. Cellular neurothekeoma has plumper spindle and epithelioid cells than dermal nerve sheath tumor and is negative for S100 protein.

Cellular Neurothekeoma

Cellular neurothekeoma is a rare, distinctive benign dermal tumor. The line of differentiation exhibited by this tumor is uncertain, though it has been presumed to be a fibroblastic/myofibroblastic or fibrohistiocytic lineage tumor.57–59 Cellular neurothekeoma affects all age groups, but its incidence peaks in the second and third decades, with female predominance. Tumors usually arise in the upper extremities, head and neck, or shoulders, and typically present as asymptomatic, slow-growing, dome-shaped nodules or masses.

Histologically, tumor cells are epithelioid to spindle shaped and arranged in a lobulated, plexiform, or focally sheetlike growth pattern (Figure 12, A and B). Myxoid change is common. Atypical features, such as nuclear atypia and pleomorphism, infiltrative growth, vascular invasion, and perineural invasion, have been described in some cases, but the presence of atypical histologic features has no clinical significance.60 The tumor cells have no specific immunophenotype, but are often positive for NKI/C3, neuron-specific enolase, and SMA.

The differential diagnosis of cellular neurothekeoma includes FH, dermal nerve sheath myxoma, and plexiform fibrohistiocytic tumor. Fibrous histiocytoma does not show areas of nested growth, which are typical of cellular neurothekeoma. In contrast to dermal nerve sheath myxoma, cellular neurothekeoma lacks S100 protein expression. Plexiform fibrohistiocytic tumor is distinguished from cellular neurothekeoma by nodules containing mononuclear histiocytoid cells and osteoclast-like giant cells and fascicles of spindled (myo)fibroblastic cells.61

Plexiform Schwannoma

Plexiform schwannoma is an uncommon variant of schwannoma and is characterized by its distinctive plexiform growth pattern. It typically occurs in skin or subcutaneous tissue of the head and neck, extremities, trunk, or deep somatic soft tissue of children and young adults.62,63 Plexiform schwannoma involves multiple nerve fascicles or a nerve plexus. In contrast to plexiform neurofibroma, it is not usually associated with neurofibromatosis type 1. Rare cases of plexiform schwannoma associated with neurofibromatosis type 2 have been described.64

Histologically, plexiform schwannoma is composed of Schwann cells with a multinodular or plexiform architecture (Figure 13, A and B) with a rim of perineural cells and a thin fibrous capsule around each nodule. Nuclear palisading is observed. It is often more cellular than ordinary schwannoma. Nuclear atypia is frequent, such as ancient schwannoma.
**Figure 11.** Dermal nerve sheath myxoma. A, The tumor shows a multilobulated growth pattern separated by fibrous septa. B, Spindle, stellate, or ring-shaped tumor cells are present in prominent myxoid stroma. C, The tumor cells are positive for S100 protein (hematoxylin-eosin, original magnifications ×4 [A] and ×200 [B]; original magnification ×200 [C]).

**Figure 12.** Cellular neurothekeoma. A, Low-power view shows a multilobulated or nested growth pattern. B, The tumor cells are spindle to epithelioid shaped with vesicular nuclei and eosinophilic cytoplasm (hematoxylin-eosin, original magnifications ×40 [A] and ×200 [B]).

**Figure 13.** Plexiform schwannoma. A, The tumor shows a multinodular or plexiform growth pattern composed of spindle tumor cells. B, The tumor cells have elongated, tapering nuclei and indistinct cytoplasmic borders. Nuclear palisading is observed (hematoxylin-eosin, original magnifications ×40 [A] and ×200 [B]).
Highly cellular examples of plexiform schwannoma have been reported in infants and children. Immunohistochemically, the tumor cells are diffusely positive for S100 protein and variably positive for GFAP. The perineurial cells surrounding individual tumor nodules are positive for EMA.

The differential diagnosis of plexiform schwannoma includes plexiform neurofibroma and malignant peripheral nerve sheath tumor (MPNST). Plexiform neurofibroma is distinguished from plexiform schwannoma by hyperplastic nerves, more uniform spindle cells, collagen bundles, and abundant myxoid stroma. Cellular examples of plexiform schwannoma can mimic MPNST, but MPNST shows anaplasia, mitoses, and necrosis, and lacks encapsulated nodules and strong S100 protein expression.

**BIPHASIC PATTERN: MYOFIBROMA/MYOPERICYTOMA**

Myofibroma is an uncommon, benign neoplasm that exhibits perivascular myoid differentiation. Most commonly, tumors arise in infants and children, but they can develop at any age. Myofibroma occurs commonly in the dermis or subcutis of the head and neck, trunk, and extremities, and can be solitary or multicentric (myofibromatosis). Familial forms have been reported with autosomal dominant inheritance.

Histologically, myofibroma shows a characteristic biphasic pattern composed of (1) myoid nodules of eosinophilic spindled cells and (2) smaller, ovoid primitive cells with scanty cytoplasm associated with thin-walled, branching blood vessels (Figure 14, A and B). A small set of myofibromas may display atypical features, such as a highly cellular fibrosarcoma-like area, infiltrative growth, absent myoid nodules, intravascular invasion, and perineural invasion. Immunohistochemically, myoid spindle cells are positive for SMA and usually negative for desmin.

Myopericytoma is a benign tumor showing perivascular myoid differentiation that forms a morphologic continuum with myofibroma, so-called infantile hemangiopericytoma, angioleiomyoma, and glomus tumors. Myopericytomas arise predominantly in the extremities, head and neck, and trunk of adults. Histologically, tumors are composed of...
ovoid or spindle-shaped cells with eosinophilic cytoplasm arranged in a perivascular concentric pattern. Most cases behave in a benign fashion, but malignant examples of myopericytoma have rarely been reported.69

The differential diagnosis of myofibroma includes nodular fasciitis, leiomyoma, FH, and myopericytoma. Nodular fasciitis contains looser fascicles with variably prominent myxoid stroma. Leiomyoma lacks a biphasic pattern. Fibrous histiocytoma has a storiform pattern. Myopericytoma lacks the conspicuous biphasic pattern of myofibroma. If the distinction between myofibroma and myopericytoma is unclear, the term myofibroma/myopericytoma may be designated.

NONMESENCHYMAL NEOPLASMS MIMICKING CUTANEOUS SPINDLE CELL MESenchymAL TUMORS

Spindle Cell Squamous Cell Carcinoma

Squamous cell carcinoma is a common malignant neoplasm of the skin in which the tumor cells show squamous differentiation. Spindle cell squamous cell carcinoma is a rare variant of squamous cell carcinoma, and is characterized by a wholly or predominantly spindle cell component.70,71 Spindle cell squamous cell carcinoma arises most often in sun-exposed skin of elderly patients, and presents as a plaque or nodule.

Histologically, spindle cell squamous cell carcinoma is composed of relatively uniform spindle cells. The tumor cells have oval, vesicular nuclei with prominent nucleoli and plump eosinophilic cytoplasm, and are arranged in sheets or fascicular or focal storiform patterns (Figure 15, A). Nuclear atypia and pleomorphism are present, and mitoses are frequently observed. The tumor cells are positive for epithelial markers (eg, cytokeratin AE1/AE3, EMA, CAM5.2, cytokeratin 5/6, p63, and p40 (Figure 15, B). Immunohistochemical markers are focally positive or entirely negative in up to 30% of cases, and thus a panel of appropriate antibodies is diagnostically useful.

The differential diagnosis of spindle cell squamous cell carcinoma includes AFX and PDS, spindle cell melanoma, and other sarcomas. Atypical fibroxanthoma lacks typical squamous differentiation and is negative for cytokeratins. Spindle cell melanoma is positive for S100 protein. For malignant spindle cell neoplasms arising in the skin and mucosal sites, suspicion of spindle cell squamous cell carcinoma should be considered in differential diagnosis before diagnosing sarcoma. The presence of dysplasia or squamous cell carcinoma in situ of overlying or adjacent epithelium, foci showing squamous differentiation, and a nested growth pattern are helpful diagnostic clues.72

Desmoplastic Melanoma

Desmoplastic melanoma is a rare variant of malignant melanoma and is characterized by a spindle cell pattern and stromal fibrosis. It occurs most commonly in the head and neck region of older patients, exhibits slight male predominance, and presents as a slowly growing nodule or broader plaque.73,74 Desmoplastic melanoma has high rates of local recurrence, and metastasis to the lung is relatively common.75

Histologically, desmoplastic melanoma is an ill-defined lesion composed of spindle tumor cells with collagenous stroma. The tumor cells have elongated, wavy, or tapered nuclei with scanty cytoplasm; they are arranged in a fascicular pattern, and merge with scarlike area. Cellularity and nuclear atypia can vary (Figure 16, A and B). Mitoses are often scanty. The tumor cells often infiltrate around the deep skin adnexa, and are observed closely around and within nerves. Lymphoid aggregates are also present. Immunohistochemically, the tumor cells are strongly positive for S100 protein (Figure 16, C). HMB-45 and Melan-A are usually negative, but can occasionally be positive. SOX10 is a useful marker of desmoplastic melanoma.76

The differential diagnosis of desmoplastic melanoma includes scar, cutaneous FH, MPNST, and sarcomas. Scars show myofibroblastic proliferation, collagen bundles oriented parallel to epidermis, and verticalized blood vessels. Cutaneous FH shows collagen entrapment and overlying epidermal hyperplasia and lacks significant cytologic atypia. In contrast to MPNST, desmoplastic melanoma involves the papillary dermis and is diffusely positive for S100 protein. The presence of abnormal melanocytic...
proliferation, atypical spindle cells associated with dense stromal fibrosis, and dermal lymphoid aggregates should raise suspicion of desmoplastic melanoma. The diagnosis is confirmed by immunohistochemical studies for ST00 protein and SOX10.

CONCLUSIONS

This review summarizes the pathologic features and differential diagnosis of common cutaneous spindle cell neoplasms according to their architectural patterns. A pattern-based approach combined with ancillary studies including immunohistochemistry and molecular testing aids accurate diagnosis. The diagnosis of spindle cell squamous cell carcinoma and desmoplastic melanoma should always be considered and excluded when a cutaneous spindle cell neoplasm is encountered. Strict diagnostic criteria should always be applied to avoid misdiagnosis. Further study of the molecular pathogenesis and classification of unrecognized cutaneous neoplasms is needed.

The authors thank Helen Chiffotides, PhD, and Kathryn Stockbauer, PhD, for their excellent editorial help. This work was supported by the 2017 Yeungnam University Research Grant.