Cutaneous and Superficial Soft Tissue CD34⁺ Spindle Cell Proliferation

Hongyu Yang, MD, PhD; Limin Yu, MD, MS

Context.—Cutaneous and superficial soft tissue spindle cell proliferations with CD34 expression represent a unique heterogeneous group of lesions. They can pose diagnostic challenges for unaware pathologists in their daily practice.

Objective.—To review selected entities of CD34⁺ spindle cell proliferations in the skin and superficial soft tissue. The effective diagnostic approaches using clinical, histopathologic, and immunophenotypical findings are discussed within a broad spectrum of differential diagnosis.

Data Sources.—All information used in the article is obtained from published literature by PubMed search and Internet-based search engines. The authors’ collective experience and real-life examples are also used.

Conclusions.—Spindle cell proliferations with CD34 positivity can be worked up to a definitive diagnosis by using clinical, histopathologic, and immunophenotypical findings. Familiarity with these entities helps pathologists make the accurate diagnosis.


The entities we are going to discuss include classic examples, such as spindle cell lipoma, and the relatively recent or rare entities such as medallion-like dendrocyte hamartoma (plaquelike CD34⁺ dermal fibroma), cellular digital fibroma, and superficial CD34⁺ fibroblastic tumor. The key clinical/histologic/immunophenotypical features will be emphasized and differential diagnosis workup highlighted.

CELLULAR DIGITAL FIBROMA

Example 1

A 60-year-old man presented with a wartlike small lesion in his right index finger of 10 months’ duration that slowly increased in size. On examination, the lesion was a small, dome-shaped, painless pink papule measuring 5 mm in diameter, which was present proximal to nail fold on the dorsal aspect of his right index finger. A punch biopsy was performed and the histologic evaluation revealed a polypoid tumor showing a dermal spindle cell proliferation. The spindle cells were arranged in short fascicles and intersecting bundles embedded in a slightly myxoid background (Figure 1, A). No nuclear atypia or mitosis was seen. The lesional cells were strongly positive for CD34 (Figure 1, B) and negative for S100, epithelial membrane antigen (EMA), and Factor XIIIa. The lesion appeared to be incompletely removed by the punch biopsy procedure; there was no recurrence after 18-month follow-up.

Diagnosis: Cellular Digital Fibroma

At the acral sites such as the fingers and toes, there are many entities involving the dermis and subcutis with spindle cell proliferations of either fibroblastic or fibroblastic/myofibroblastic lineages. Because most of the entities present with a broad clinical and histopathologic spectrum, they frequently pose diagnostic challenges to the pathologists who are not familiar with them. We will...
review the newly described cellular digital fibroma and its mimickers.

**Clinical Features**

McNiff and colleagues described a unique subset of digital fibromas in their daily and consultation practice. The lesions clinically presented as slow-growing, small nodules (≤0.5 cm) and most of them resembled warts. All patients were adults aged from 33 to 83 years (average, 54 years) with no sexual preference (male to female ratio = 3:4). The predominant involvement sites were the fingers and toes (11 of 14 cases, 78.6%). All cases showed an indolent behavior with no recurrence after complete excision in the cases with clinical follow-up.

**Histopathologic Features**

All the cellular digital fibromas demonstrate a proliferation of uniform slender fibroblasts forming short intersecting fascicles oriented in parallel or sometimes in a haphazard fashion in the upper reticular dermis, associated with variably dense dermal collagen. Sometimes the stroma can be myxoid, with uniform spindle cells showing wavy features and arranged in a storiform “whorled” pattern. No pleomorphism is present, and no increased mitosis is seen.

A striking feature of this set of acral spindle cell lesions is that the dermal spindle cells stain strongly for CD34 in all cases studied so far. The spindle cells are negative for S100, EMA, and Factor XIII.

**Differential Diagnosis**

Given its clinical presentation and dermal spindle cell proliferation with CD34 positivity, several spindle cell neoplasms enter into the differential diagnosis, especially the following entities.

**Superficial Biopsy of Early Dermatofibrosarcoma Protuberans.**—When the biopsy is superficial, it can be challenging to distinguish DFSP from cellular digital fibroma solely on the basis of histologic findings. The clinical presentation can help differentiate these 2 entities. Dermatofibrosarcoma protuberans rarely occurs in the digits of adults and normally presents as plaques with slow growth. The common clinical presentation of cellular digital fibroma is small papules (≤0.5 cm) on the fingers or toes. In difficult cases, cytogenetic and molecular analysis of the COL1A1-PDGFB gene arrangement is helpful because this change is a highly specific genetic hallmark of DFSP.

**Superficial Acral Fibromyxoma (Digital Fibromyxoma).**—This is an entity closely mimicking cellular digital fibroma. Some authors even consider that they are the same entity in a spectrum. Both are acral lesions characterized by delicate CD34+ spindled cells in a variable stroma. In general, superficial acral fibromyxomas are larger (0.5–5 cm in diameter), slow-growing, asymptomatic tumors that commonly present as solitary lesions with close proximity to nail matrix. Compared with cellular digital fibroma, superficial acral fibromyxomas have a distinct myxoid stroma, increased vascularity, less cellularity, and conspicuous mast cells. Meanwhile, keratin horn and epidermal collarette are commonly observed in cellular digital fibroma. Even though both are strongly positive for CD34, superficial acral fibromyxoma is usually positive for CD99 and

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**Table 1. CD34+ Spindle Cell Neoplasms and Their Differential Diagnoses**

<table>
<thead>
<tr>
<th>Fibrohistiocytic and fibroblastic neoplasm</th>
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<tr>
<td>Dermatofibrosarcoma protuberans and giant cell fibroblastoma</td>
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<td>Myxoinflammatory fibroblastic sarcoma</td>
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<td>Solitary fibrous tumor</td>
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<td>Giant cell angiofibroma</td>
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<td>Lipofibromatosis</td>
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<td>Fibroma</td>
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<td>Superficial angiofibroma</td>
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<td>Superficial acral fibromyxoma</td>
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<td>Cellular digital fibroma</td>
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<td>Cellular angiofibroma</td>
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<td>Superficial CD34+ fibroblastic tumor</td>
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<td>Neural neoplasms</td>
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<td>Neurofibroma</td>
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<td>Nerve sheath myxoma</td>
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<td>Perineurioma</td>
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<td>Lipogenic neoplasms</td>
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<td>Spindle cell lipoma/pleomorphic lipomas</td>
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<td>Neoplasms of unknown lineage</td>
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<tr>
<td>Pleomorphic hyalinizing angiectatic tumor of soft parts</td>
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<tr>
<td>Epithelioid sarcoma</td>
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**Figure 1.** Cellular digital fibroma. A, Histologic features. B, Diffuse positivity of CD34. Courtesy of Ling Xia, MD, Manitowoc, Wisconsin (hematoxylin-eosin, original magnification ×100 [A]; original magnification ×200 [B]).
sometimes positive for EMA, while cellular digital fibroma is negative for both markers.9

Dermatofibroma.—Dermatofibroma is very rare at the acral sites. It is composed of classical plump and/or angulated fibroblasts in storiform arrays with entrapped collagen at the periphery, in contrast to the more fascicular growth pattern seen in cellular digital fibroma. Dermatofibroma frequently shows giant cells and hemosiderin deposition. The dermatofibroma cells are positive for Factor XIIIa and negative for CD34.

Perineurioma.—Some histologic features of cellular digital fibroma, such as delicate spindle cells arranged in intersecting short fascicles and focal whirling growth pattern, can be seen in perineurioma. Perineurioma is normally present in the subcutis with some lesions present entirely in the dermis. The cells in perineurioma are more epithelioid and can have a striking “onion-skin” growth pattern. In difficult cases, immunohistochemical studies are helpful. The cells in perineurioma are negative for CD34, especially at the acral sites,15–17 but strongly positive for EMA, while cellular digital fibroma cells are strongly positive for CD34 and negative for EMA. Other neural neoplasms in the differential diagnosis can be easily ruled out by their positive S100 staining.

Other Digital Fibromas Including Acral and Subungual Angiofibroma, Acquired Digital Fibrokeratoma, and Acquired Reactive Digital Fibroma.—Acquired digital fibrokeratoma (ADF) is normally a polypoid acral lesion histologically showing vertically oriented collagen and fibrocytes in the dermis, which are typically encased by the anacanthotic, hyperkeratotic epidermis. Acral and subungual angiofibromas, which are sometimes included within the spectrum of ADF, are present with occasional dilated vessels within fibrotic dermis containing plump fibroblasts. The cells in both ADF and angiofibroma are negative for CD34 and positive for Factor XIIIa. Acquired reactive digital fibroma is an entity recently described by Plaza et al.18 It has been exclusively reported in male patients with a strong history of trauma. Histologically, it shows a proliferation of spindle cells that are positive for vimentin and rarely positive for CD34 and are negative for other markers including S100, EMA, Factor XIIIa, CD99, smooth muscle actin, desmin, h-caldesmon, CD68, and β-catenin.

In summary, cellular digital fibroma is a newly introduced CD34+ spindle cell fibroblastic lesion that predominantly involves the acral sites. In general, it appears to be a benign lesion owing to its small size, unremarkable cytology, and absence of recurrence in the cases studied. It has a unique immunohistochemistry profile with strong CD34 positivity, which is different from other reported digital fibromatous lesions. Superficial biopsy of DFSP is in the differential diagnosis, which needs be ruled out by clinical-pathologic correlation.

SUPERFICIAL CD34+ FIBROBLASTIC TUMOR

Example 2

A 40-year-old white man presented with a skin-colored 2.5-cm mass on his right thigh of 3 years’ duration. It was nontender and slowly increased in size. An excision of the lesion showed a relatively circumscribed deep dermal-based tumor with infiltrative growth into the subcutis (Figure 2, A). The tumor was composed of spindle to epithelioid cells, arranged in a solid sheetlike or fascicular growth pattern, showing focal prominent nuclear pleomorphism and granular cytology (Figure 2, B). Scattered mixed inflammatory cells including lymphocytes, xanthomatous histiocytes, and mast cells were observed throughout the tumor (Figure 2, C). The lesional cells were strongly positive for CD34 (Figure 2, D), and focal weak staining of pankeratin was also seen. No positivity was seen in melanocytic, myogenic, and neural markers.

Diagnosis: Superficial CD34+ Fibroblastic Tumor

In 2013, Carter and colleagues12 studied 18 cases of low-grade fibroblastic tumor of the superficial soft tissue that have distinctive clinical and pathologic features not described in previous literature. They coined the term superficial CD34+ fibroblastic tumor owing to its strong diffuse CD34 positivity. Since then, additional case reports have also been published.19,20

Clinical Features

All the tumors studied ranged from 1.5 to 10 cm (mean, 4.1 cm) and presented as a slow-growing, painless mass most commonly in the lower extremity (the thigh, buttock, lower leg, and foot). Other sites also included the arm, shoulder, and groin. They occurred exclusively in adults (median age, 38 years; range, 20–76 years) with no sex preference (10 males and 8 females). The neoplasms were within the superficial subcutaneous soft tissue with minimal or no involvement of deep musculature. Most tumors behaved in an indolent fashion. Of 13 patients available for clinical follow-up ranging from 1 to 104 months (median, 24 months), 12 had no disease recurrence. Only 1 patient (7.7%) had a regional lymph node metastasis 7 years after presentation.

Pathologic Features

Grossly, the tumor is most often described as a firm, tan-yellow, and sometimes gelatinous mass. It is relatively circumscribed but may have peripheral infiltrative growth into surrounding fat tissue. The major characteristics of this tumor include the following.

“Alarming” Nuclear Pleomorphism.—The tumor is composed of moderately cellular fascicles and sheets of spindle to epithelioid cells with abundant granular and sometimes glassy cyttoplasm. Xanthomatous changes can be present. Most of the cells have striking nuclear pleomorphism with bizarre lobated and hyperchromatic nuclei containing multiple large prominent nucleoli. Cytoplasmic/nuclear pseudoinclusions can also be found.

Paradoxically Low Mitotic Count and Proliferation Index.—Despite the extreme degree of nuclear atypia, the mitotic figures are uncommon (<1/50 high-power fields). Atypical mitotic figures are absent. Ki-67 labeling proliferation index is exceptionally low (<1% of the tumor cells).

Background of Chronic Inflammatory Cell Infiltrate.—There are usually moderate amounts of chronic inflammatory cells present within the tumor, including lymphocytes and mast cells.

Strong and Diffuse Positivity for CD34.—All tumors showed strong and diffuse CD34 positivity. Focal weak positivity for keratin is observed in about 70% of cases studied. Other markers including FLI-1, ERG, S100, desmin, smooth muscle actin (SMA), and TP53 are negative in all tested cases. There is no loss of nuclear expression of INI-1 (SMARCB1). The cases tested by fluorescence in situ hybridization (FISH) for TGFBR3 and/or MGEA5 rearrangements have all been negative.12

CD34+ Spindle Cell Proliferation—Yang & Yu
Differential Diagnosis

Owing to the high-grade “alarming” cell morphology as well as strong CD34 positivity in superficial CD34+ fibroblastic tumor, a number of intermediate- to high-grade sarcomas, in addition to benign mesenchymal tumors, must be included in the differential diagnosis workup (Table 2).

Undifferentiated Pleomorphic Sarcoma (Previously Known as Malignant Fibrous Histiocytoma), Atypical Fibroxanthoma, and Myxofibrosarcoma.—These tumors all have striking nuclear pleomorphism similar to superficial CD34+ fibroblastic tumor. Undifferentiated pleomorphic sarcoma often involves the deeper soft tissue, while atypical fibroxanthoma often occurs in the sun-exposed areas and is a dermal-based tumor. Myxofibrosarcoma typically arises in the superficial soft tissue of the extremities; it is characterized by the presence of myxoid nodules displaying an arborizing, thick-walled vasculature. These entities can be easily distinguished from superficial CD34+ fibroblastic tumor, which usually shows the paradoxical low mitotic count, low Ki-67 proliferation index, as well as strong CD34 expression. They also lack the distinct cytoplasmic and nuclear features of superficial CD34+ fibroblastic tumor. Coexpression of cytokeratin and CD34 is not a feature of myxofibrosarcoma; however, in one report, about half of the superficial myxofibrosarcomas studied show CD34 positivity, making this a diagnosis pitfall. Finally, TP53 shows strong positivity in high-grade pleomorphic sarcoma, atypical fibroxanthoma, and myxofibrosarcoma, while overexpression of TP53 is absent in superficial CD34+ fibroblastic tumor.

Myxoinflammatory Fibroblastic Sarcoma (Also Called Inflammatory Myxohyaline Tumor of Distal Extremities).—Myxoinflammatory fibroblastic sarcoma (MIFS) and superficial CD34+ fibroblastic tumor share some morphologic features such as bizarre-appearing nuclei with prominent nucleoli, low mitotic rate, rare cytokeratin expression, and prominent chronic inflammatory cell infiltrate within the tumor. However, MIFS mostly occurs at the acral sites with prominent myxoid background, negativity for CD34, and rearrangements of TGFBR3 and MGEA5 genes.

Pleomorphic Hyalinizing Angiectatic Tumor.—Pleomorphic hyalinizing angiectatic tumor (PHAT) comes into the differential diagnosis owing to its similar superficial location and paradoxical striking nuclear pleomorphism with low mitotic count. However, the characteristic features...
of PHAT, such as ectatic hyalinized blood vessels and abundant hemosiderin deposition, are absent in superficial CD34+ fibroblastic tumor.10

**Dermatofibrosarcoma Protuberans.**—The irregular infiltrating growth pattern and strong diffuse CD34 positivity, especially in the less pleomorphic spindle cell areas, of superficial CD34+ fibroblastic tumor can mimic DFSP. However, the alarming cytologic atypia is not commonly seen in DFSP.

**Epithelioid Sarcoma or Epithelioid Endothelial Cell Tumor.**—The coexpression of CD34 and cytokeratin of superficial CD34+ fibroblastic tumor can be seen sometimes in epithelioid sarcoma and other vascular neoplasms. However, epithelioid sarcoma typically shows granuloma-like areas around necrosis and central hyalinization with loss of INI-1 (SMARCB1) expression.28 The vascular tumors are easily separated by their positive staining for the vascular markers CD31, FLI-1, and ERG.

In summary, this is a newly described entity with the risk of overdiagnosis as a high-grade sarcoma and subsequent unnecessary treatments. The unique features of this lesion include suprafascial location, striking nuclear pleomorphism, paradoxical low mitosis/low Ki-67 proliferation index, strong CD34 expression, and indolent clinical behavior.

### SPINDLE CELL LIPOMA

**Example 3**

A 50-year-old man presented with a 3.0-cm, slow-growing mass in his right shoulder. The mass was nontender and movable. It had gradually increased in size in the previous 3 years. An excisional biopsy was performed. It was a 3.0 × 2.0 × 1.5-cm, relatively well-circumscribed, nonencapsulated spindle cell tumor with a tan-yellow cut surface in the deep dermis and superficial subcutis (Figure 3, A). The spindle cells were relatively monotonous with no significant pleomorphism. They were arranged in short fascicles and separated by “ropey” collagen bundles (Figure 3, B). Occasional intermixed mature adipocytes and background myxoid stroma background were present (Figure 3, C). The spindle cells were uniformly positive for CD34 (Figure 3, D) and negative for S100, SMA, and desmin. No necrosis or hemorrhage was present. There was no recurrence of the lesion at 8-month follow-up visit.

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**Table 2. Characteristics of Differential Diagnosis Entities Mimicking Superficial CD34+ Fibroblastic Tumor**

<table>
<thead>
<tr>
<th>Disease Entity</th>
<th>Clinical Presentation</th>
<th>Histopathologic Features</th>
<th>Immunohistochemistry</th>
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<tbody>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>Deep-seated soft tissue tumor mostly in lower extremities</td>
<td>Proliferation of pleomorphic cells with marked nuclear atypia and increased mitosis with high Ki-67 labeling proliferation index</td>
<td>Diagnosis based on exclusion of other high-grade sarcoma with specific lineage differentiation, such as muscle, melanocytic, neural by respective markers; CD34 can show variable positivity, but positive staining is not helpful for diagnosis</td>
</tr>
<tr>
<td>Atypical fibroxanthoma</td>
<td>Dermal-based tumor in sun-exposed areas (head and neck)</td>
<td>Proliferation of marked atypical cells with pleomorphic nuclei and xanthomatous cytoplasm with increased mitosis and Ki-67 labeling proliferation index</td>
<td>Diagnosis is based on exclusion of spindle cell squamous carcinoma (negative P63 or high-grade keratin 34be12), melanoma (negative for S100, Mart-1, or HMB-45), and leiomyosarcoma (negative for desmin); CD34 usually shows negativity</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>Predominantly in extremities, with ½ developing in the dermis and subcutis</td>
<td>Multinodular tumor composed of pleomorphic spindle cells in myxoid background; curvilinear vessels (thick walled with broad arc) with condensation of cells around vessels is characteristic</td>
<td>No specific stains exist, but ½ to ½ of cases of superficial myxofibrosarcoma can have CD34 positivity; negative for S100</td>
</tr>
<tr>
<td>Myxoinflammatory fibroblastic sarcoma</td>
<td>Distal extremities (hand and feet), dermis and subcutis</td>
<td>Virocyte or Reed-Sternberg–like cell proliferation in a background of acute and chronic inflammatory cells and stromal fibrosis; multinodular tumor of polymorphous cells with infiltrative margins</td>
<td>Less helpful for diagnosis; it can be positive for vimentin and sometimes CD34 and CD68</td>
</tr>
<tr>
<td>Pleomorphic hyalinizing angiectatic tumor</td>
<td>Subcutis or deep dermis, most in extremities and trunk</td>
<td>Characterized by ectatic blood-filled vessels surrounded by hyalinized stroma and atypical pleomorphic spindle cells that contain hemosiderin and cytoplasmic inclusions (malignant fibrous histiocytoma-like cells), low mitotic activity</td>
<td>Positive for vimentin, CD34, and CD99; negative for S100 and CD31; Ki-67 &lt; 2%</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>Distal extremities of young adults; most often located in reticular dermis and sometimes in subcutis</td>
<td>Epithelioid tumor cells in granuloma annulare–like fashion around areas of necrosis and central hyalinization</td>
<td>Positive for epithelial markers such as keratin and EMA, positive for CD34, and rarely CD31; negative for INI1/SMARCB1</td>
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Abbreviation: EMA, epithelial membrane antigen.
Diagnosis: Spindle Cell Lipoma (Low-Fat Type)

Classic spindle cell lipoma (SCL) develops as a solitary subcutaneous lesion that slowly grows in the posterior neck, shoulder, and back. The tumor usually measures 3 to 5 cm. It occurs most frequently in adult males in their 40s to 60s. Histologically, SCL is a well-circumscribed tumor in the dermis and subcutis. It is composed of mature adipocytes, and spindle cells in myxoid matrix. The spindle cells are cytologically bland and CD34⁺, arranged in short fascicles in a so-called school of fish pattern. Ropey collagen (thick refractile eosinophilic collagen) is a characteristic feature. The ratio of the mature fat to the spindle cells can vary significantly. Infrequently, fat is present in a small amount in “low-fat” and “fat-free” SCL, which can disguise the tumor’s lipomatous nature and cause diagnostic challenges. The key to the accurate diagnosis is to recognize the spindle cells in the “low-fat” SCL, which are histologically similar to those in the classic SCL. The differential diagnosis of “low-fat” SCL is broad, including both benign and malignant neoplasms.

Neurofibroma.—Neurofibroma is an ill-defined dermal tumor composed of fascicles of spindle cells in a haphazard pattern. The spindle cells have wavy and comma-shaped nuclei. The stroma between these fascicles is fibrillar, collagenous, and sometimes myxoid. Scattered mast cells are a common finding. Although admixed CD34⁺ cells can be seen in neurofibroma, the spindle cells of neurofibroma are S100 protein positive and CD34⁻; the S100 protein expression is limited in the adipocytes of “low-fat” SCL.

Solitary Fibrous Tumor.—It can be difficult to distinguish solitary fibrous tumor (SFT) from “low-fat” SCL when the stroma is more collagenous. Solitary fibrous tumor represents a spectrum of mesenchymal tumors. It most frequently presents as a pleural tumor. When it rarely involves the skin, it presents as a firm, well-circumscribed dermal nodule. The tumor is usually seen in adults and affects both sexes equally. The head and neck region is the most common site of cutaneous SFT, although it can involve any area of the body. Cases of cutaneous SFT that have been reported to date show benign behaviors. Histologically, the tumor is a nonencapsulated, well-circumscribed dermal tumor consisting of spindle cells in fascicles or in a storiform arrangement. There is an alternation of hypercellular and hypocellular areas separated by thick and hyalinized collagens in a “patternless” pattern. The tumor cells are...
diffusely positive for CD34 and negative for S100 protein. Entrapped adipocytes can be seen,\textsuperscript{35} which can cause difficulty in differentiating SFT from “low-fat” SCL. When histologic diagnosis is challenging, correlation with clinical findings is critical. Special immunohistochemical study for STAT6 may be helpful, which is shown to be a sensitive and specific marker of SFT.\textsuperscript{36}

**Dermatofibrosarcoma Protuberans.**—The differential diagnosis of DFSP is a critical one. Dermatofibrosarcoma protuberans most commonly develops in younger patients. It is typically composed of a proliferation of plump CD34\textsuperscript{+} spindle cells in a monotonous storiform arrangement in the dermis with infiltration into the subcutis. The absence of rosy collagen in DFSP is an important histologic clue in distinguishing it from SCL.

**Well-Differentiated Spindle Cell Liposarcoma (Atypical Spindle Cell Lipomatous Tumor).**—This entity is a recently reported CD34\textsuperscript{+} low-grade malignant lipogenic neoplasm that shares some similar histologic and molecular features as SCL.\textsuperscript{37} Well-differentiated spindle cell liposarcoma (WDSL) tends to arise in the subcutis or in the superficial soft tissue. The anatomic distribution of WDSL is broader than that of SCL, including the extremities and hands. The tumor can be large, up to 10 cm in a series of cases.\textsuperscript{37} It shows a nodular or infiltrative growth pattern. The lipomatous tumor cells are enlarged, fusiform, and sometimes hyperchromatic, varying in cell size and shape. Increased multivacuolated lipoblasts with scalloped nuclei can be seen. Compared with classic SCL, there is an increased number of enlarged and atypical lipoblasts in WDSL. Spindle cell lipoma lacks the amplification and/or expression of MDM2 and CDK4, a characteristic finding of the variants of atypical lipomatous tumor. WDSL shows considerable differences in clinical presentation, histologic features, and prognosis to classic SCL. WDSL displays low-grade malignancy with local recurrence.

**PLAQUELIKE CD34\textsuperscript{+} DERMAL FIBROMA (MEDALLION-LIKE DERMAL DENDROCYTE HAMARTOMA)**

**Example 4**

A 15-year-old adolescent boy presented to the dermatology clinic concerning a tan-brown lesion in his right upper back that had been present since birth and gradually increased in size in the past 6 months. On examination, the lesion was 8 × 5 cm with well-demarcated border. The surface was tan-brown and slightly atrophied with wrinkled appearance. An excision biopsy was performed and the sections showed atrophic epidermis with a bandlike dermal spindle cell proliferation (Figure 4, A). The lesional cells were spindle shaped to plump epithelioid and arranged in a concentric “whorled” pattern showing no cytologic atypia or mitosis (Figure 4, B and C). The tumor cells were strongly positive for CD34 (Figure 4, D) and negative for S100; focal weak positivity for SMA was noted. The lesion was incompletely excised; at 1-year follow-up visit, no recurrence was seen at the biopsy site.

**Diagnosis: Plaqueline CD34\textsuperscript{+} Dermal Fibroma (Medallion-Like Dermal Dendrocyte Hamartoma)**

Plaqueline CD34\textsuperscript{+} dermal fibroma (PDF) (medallion-like dermal dendrocyte hamartoma [ML-DDH]) is a recently described cutaneous neoplasm. Rodríguez-Jurado et al\textsuperscript{38} first described it in 3 young female patients in 2004. They all characteristically presented with a medallion-like triangular, oval, or round well-circumscribed lesions on the chest and neck since birth. The lesions were brownish erythematous, slightly atrophic, finely wrinkled, and symptom-free, measuring 6 to 10 cm in their largest diameters. Skin biopsy specimens showed normal or atrophic epidermis. The dermis was significant for a spindle cell proliferation, concentrically arranged around small vessels in some areas. Increased mast cells were also seen. In 1 of the 3 cases, the spindle cell infiltrate extended into the subcutis. The spindle cells were positive for CD34, Factor XIIIa, fascin, and vimentin. Cytokeratin AE1/AE3, actin, desmin, neurofilaments, and neuron-specific enolase showed negativity. The authors proposed these lesions represented a distinct hamartomatous proliferation of dermal dendrocytes and named it *medallion-like dermal dendrocyte hamartoma.*

In the past few years, few similar lesions have been described.\textsuperscript{39–43} In a series of 5 cases of ML-DDH and 7 cases of superficial (plaquelike) DFSP, Kutzner et al\textsuperscript{44} expanded the clinicopathologic spectrum of ML-DDH. Medallion-like dermal dendrocyte hamartoma also arose on the neck and the extremities in 2 male and 3 female patients whose ages ranged from 9 to 69 years (mean, 51.8 years; median, 64 years). The lesions were clinically described as coin shaped, slightly indurated, brownish or erythematous. Histologically, the neoplasms showed a distinct blandlike proliferation of fusiform cells in the upper dermis. Only the congenital tumor in a 9-year-old boy extended into the deep dermis and into the septa of the subcutis. The tumor cells strongly expressed CD34 and were negative for Factor XIIIa and S100. From the observation that the lesions were present in both pediatric and adult patients and that the tumor cells were negative for dermal dendritic marker Factor XIIIa, Kutzner and coauthors\textsuperscript{44} believed the descriptive term of *plaque-like CD34\textsuperscript{+} dermal fibroma* was more appropriate than ML-DDH. However, some authors believed congenital lesions with the distinct clinical presentation should be kept separate from other CD34\textsuperscript{+} dermal proliferation; should future research confirm the fibroblastic origin of the lesional cells, they think the alternative name of *medallion-like CD34\textsuperscript{+} dermal hamartoma* is more appropriate.\textsuperscript{44}

**Clinical Features**

The characteristic lesion has been described as a single, round/oval, and well-defined “medallion-like” brownish erythematous atrophic patch on the chest, neck, and extremities. Most of the reported lesions are congenital, asymptomatic, and found in pediatric patients. The clinical differential diagnosis includes aplasia cutis, anetoderma and atrophoderma, and atrophic DFSP.

**Pathologic Features**

Histologic examination reveals epidermal atrophy and a bandlike dermal proliferation of spindle cells, which extends into the subcutis in some cases. The spindle cells are concentrically arranged around small vessels and nerves. In the cases reported by Kutzner et al.,\textsuperscript{44} a 2-layer pattern was observed in the spindle cell proliferation: the cells of the upper layer were oriented vertically, while those of the lower layer in an orientation horizontal to the skin surface. Normal or decreased elastic fibers are seen. There are usually an increased number of mast cells. The tumor cells consistently stain positive for CD34 and negative for S100. Factor XIIa shows positivity in the first described cases but is not expressed in the typical cases that were subsequently described.
Owing to its rarity and recent recognition, PDF/ML-DDH has been misdiagnosed as other entities. The most significant and clinically relevant differential diagnosis is congenital/atrophic DFSP, which shows intermediate malignancy with frequent local recurrence and rare metastases. The similarity in the histologic and immunohistochemical findings of DFSP and PDF/ML-DDH can be challenging for pathologists in making an accurate diagnosis. For example, atrophic DFSP was initially diagnosed in a 6-year-old Korean girl who presented with a solitary congenital 4.0-cm plaque of CD34 diffusely positive spindle cell dermal proliferation. A final diagnosis of PDF/ML-DDH was made in the subsequent excisional specimen. Three cases of misdiagnosed PDF/ML-DDH were reported by Marque et al. Congenital atrophic DFSP was first diagnosed in an 18-month-old girl, a 14-month-old boy, and an 8-year-old girl; a diagnosis of PDF/ML-DDH was rendered in these patients after subsequent review. Cyto genetic and molecular analysis can help distinguish PDF/ML-DDH from congenital DFSP. To date, no cytogenetic profile has been reported in PDF/ML-DDH. In contrast, the COL1A1-PDGFB gene arrangement is a highly specific genetic hallmark of DFSP, present in most DFSP cases.

The detection rate is variable, dependent upon the tissue type (fresh versus formalin-fixed, paraffin-embedded) and methods (reverse transcription–polymerase chain reaction [RT-PCR] versus FISH). It has been shown that FISH analysis has a higher sensitivity than RT-PCR in archival formalin-fixed, paraffin-embedded specimens.

A PDF/ML-DDH case was initially misdiagnosed as neurofibroma. A 9-year-old boy presented with a solitary congenital patch on the nape of the neck. The lesion was atrophic, wrinkled, and pliable pink-yellow, measuring 4.5 × 8.0 cm. The skin biopsy showed a spindle cell proliferation that was negative for S100 and positive for neuron-specific enolase. The patient was diagnosed with neurofibroma and followed up for possible neurofibromatosis. Two years later, the case was reevaluated and further immunohistochemical studies showed the spindle cells were positive for CD34. The diagnosis of PDF/ML-DDH was then confirmed.

CONCLUSIONS

The ever-increasing list of spindle cell neoplasms presents great diagnostic challenges in the daily practice of pathologists. Particularly, the differential diagnosis for a...
CD34+ dermal or superficial soft tissue spindle cell neoplasms can be broad and daunting. An index consult case reported by Pitha et al. in the American Journal of Dermatopathology clearly illustrates the nature of these lesions, with different expert opinions (that case maybe fits into the later described cellular digital fibroma discussed in this article). Clinical, histopathologic, and immunohistochecmical or even molecular combined approaches are needed to overcome diagnostic challenges and render an accurate diagnosis.

References


