Fibroblastic/Myofibroblastic Tumors

5

Fibroblastic and myofibroblastic tumors represent a large group of soft tissue neoplasms that are made up of cells resembling those found in tendons or ligaments. Fibroblasts appear as spindle cells with elongated nuclei and variable amounts of associated eosinophilic collagen deposition (Fig. 5.1). Myofibroblasts can be spindled or star-shaped and demonstrate some muscle-type antigens (e.g. smooth muscle actin) by immunohistochemistry. The behavior of these tumors can span from completely benign to malignant [1].

5.1 Nodular Fasciitis and Similar Lesions

Nodular fasciitis is a lesion that typically presents in the subcutaneous tissue of adults in the third to fifth decade of life. It most commonly occurs in the upper extremities but can also arise in the head and neck and trunk, among other areas. Because nodular fasciitis can rapidly enlarge over the course of weeks, patients and their physicians can become quite concerned about an aggressive neoplasm, prompting biopsy. Over time, the growth of these tumors typically plateaus and they reach a size of no more than 3 cm in greatest dimension [2–4].

Pathology

Grossly, nodular fasciitis appears to be well circumscribed and gelatinous or fibrous in consistency. The microscopic features are thought to depend on the age of the lesion. If biopsied soon after onset, the slides show a haphazard arrangement of slender fibroblasts in the background of myxoid material (Fig. 5.2a). This is sometimes referred to as a "tissue culture" appearance, given the morphologic similarity to viral cultures in a microbiology lab. Background inflammation, focal areas of microhemorrhage, and mitosis can be seen (Fig. 5.2b). Multinucleated giant cells

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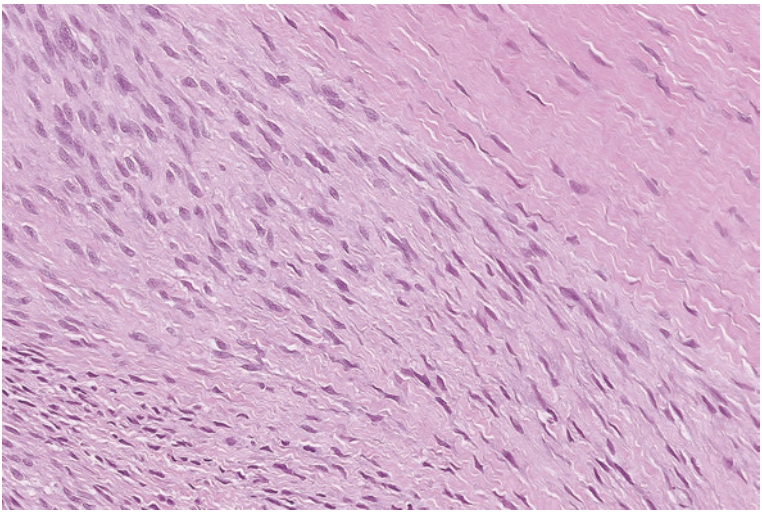

Fig. 5.1 Fibroblastic cells of superficial fibromatosis with elongated and slender nuclei with varying amounts of associated collagen

can often be identified. Lesions of medium duration are more cellular and lose their myxoid appearance. Long-standing lesions often exhibit dense sclerosis reminiscent of a scar [4].

Neoplasms similar to nodular fasciitis

- Proliferative fasciitis and proliferative myositis are benign rapidly growing lesions that occur in the extremities of adults and have a somewhat similar morphologic appearance to nodular fasciitis. These lesions can also have large epithelioid or ganglion-like cells with enlarged nuclei and conspicuous nucleoli (Fig. 5.3a) [5].
- Ischemic fasciitis occurs in older adults who have limited mobility. They tend to arise at bony prominences such as the shoulder. In addition to a haphazard arrangement of myofibroblasts, these lesions also contain juxtaposed areas of necrosis and scattered ganglion-like cells, similar to those seen in proliferative fasciitis (Fig. 5.3b) [6, 7].

Ancillary Studies

- Nodular fasciitis manifests chromosomal translocations involving the *USP6* gene.
- The *USP6* translocation can be detected by FISH.

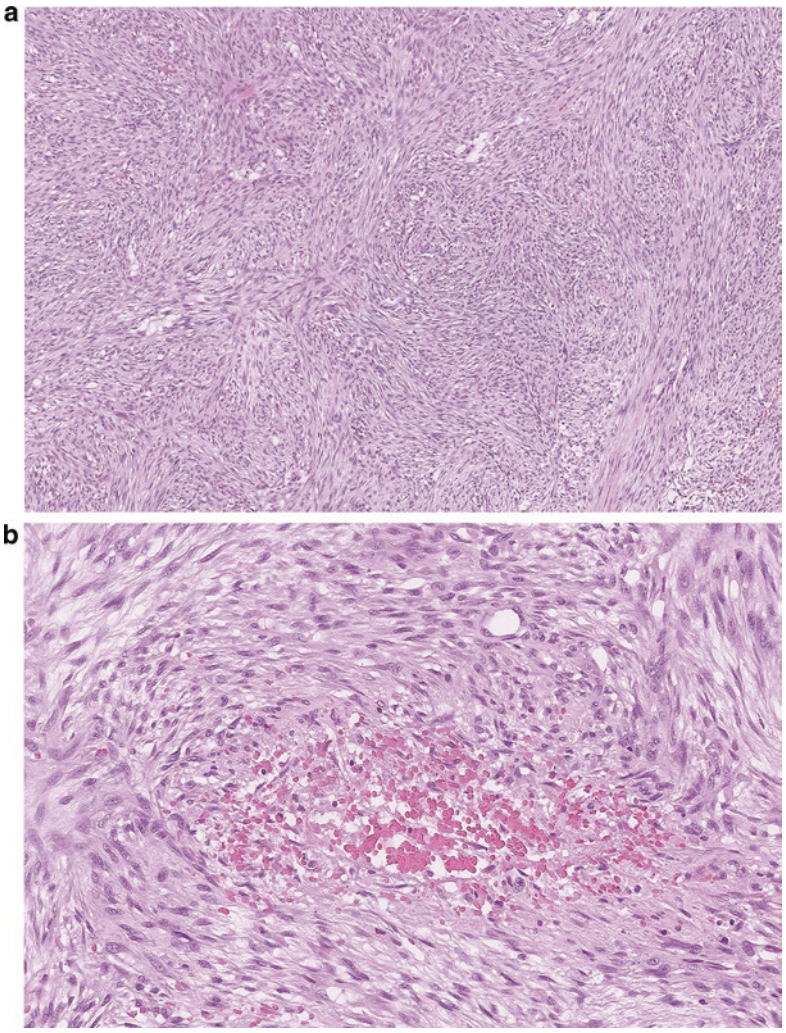

Fig. 5.2 (**a**) Nodular fasciitis with haphazard arrangement of fibroblastic cells. (**b**) Area of micro-hemorrhage in nodular fasciitis

Differential Diagnosis

- Myxofibrosarcoma
- Low-grade myofibroblastic sarcoma
- Superficial or deep fibromatosis
- Fibroma of tendon sheath

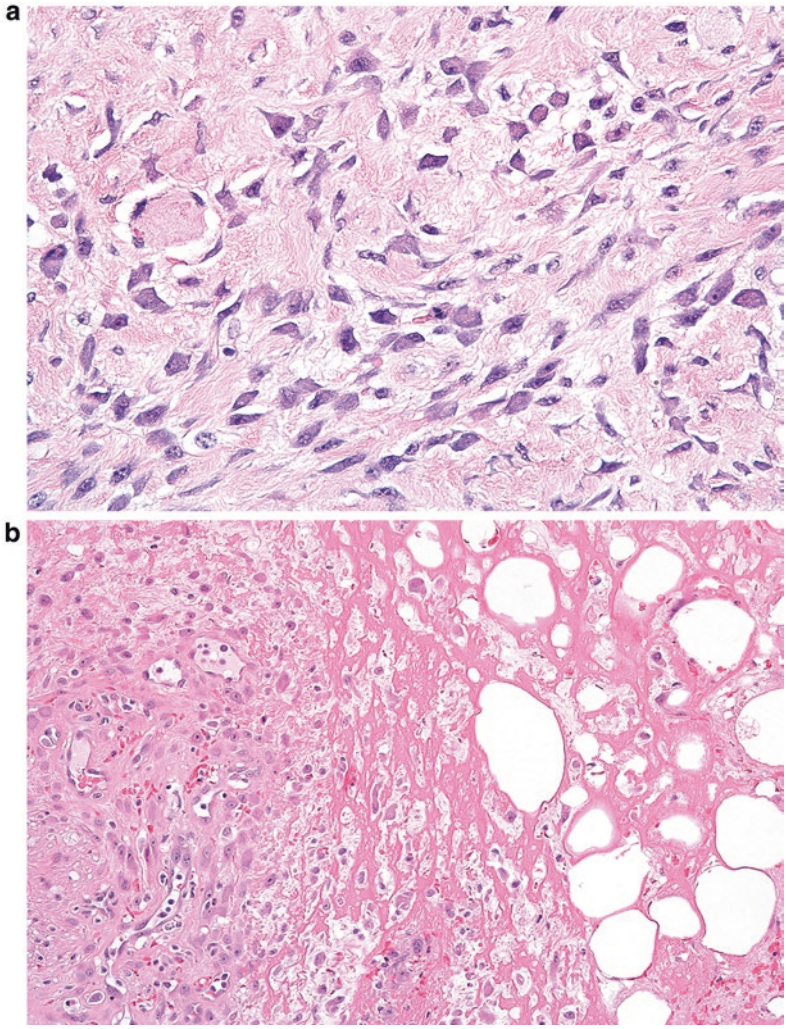

Fig. 5.3 (**a**) Proliferative fasciitis with plump epithelioid- or ganglion-like cells. (**b**) Ischemic fasciitis with area of necrosis and scattered plump epithelioid cells

Comment

1. Nodular fasciitis often presents as a rapidly growing lesion that displays disorganized spindle cells and multiple mitoses. This morphology and clinical presentation can be mistaken for more aggressive lesions such as myxofibrosarcoma, low-grade myofibroblastic sarcoma, and fibromatosis.
2. However, nodular fasciitis is usually smaller in size and lacks the atypical mitoses seen in these more aggressive neoplasms.

3. Although fibromatosis can have focal areas resembling nodular fasciitis, it typically is more infiltrative in nature.
4. Nodular fasciitis is a benign lesion that almost never recurs.
5. Recurrent lesions originally diagnosed as nodular fasciitis should be carefully assessed for features of a sarcoma. In difficult cases, FISH studies for *USP6* can help confirm the diagnosis of nodular fasciitis.

5.2 Fibroma of Tendon Sheath

Fibromas of the tendon sheath arise in adult patients between the third and fifth decades of life and typically measure less than 2 cm in size [1, 8]. They present as slow-growing nodules that are attached to the tendons of the hands or feet. The thumb, index, and middle finger are the digits most commonly involved, and some patients can experience tenderness or limited range of motion in the involved digit [9, 10]. Given the location, these are often clinically presumed to be ganglion cysts [11].

Pathology
Grossly, fibroma of tendon sheath appears as a fibrous nodule. The microscopic sections display single or multiple lobules of stellate cells with extensive amounts of associated dense sclerosis (Fig. 5.4). Compressed vascular spaces are often located at the periphery of the lesion (Fig. 5.5). Although frequently hypocellular, there can be focally more cellular areas that appear similar to nodular fasciitis [1].

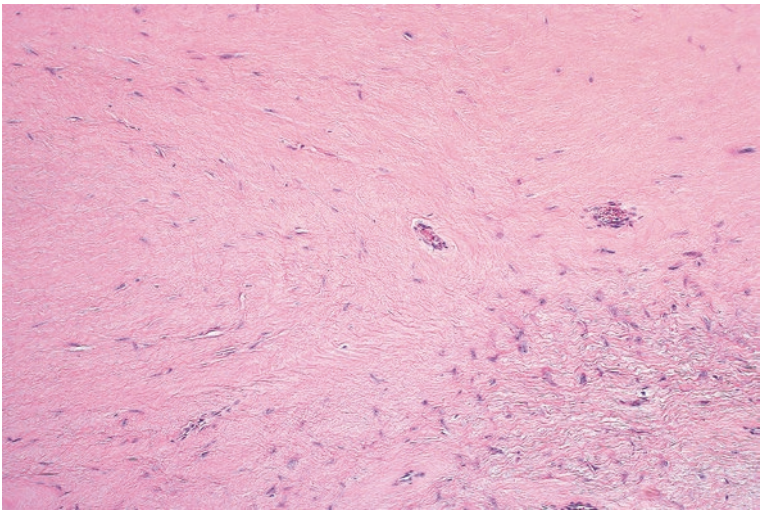

Fig. 5.4 Fibroma of tendon sheath with stellate cells and dense fibrosis

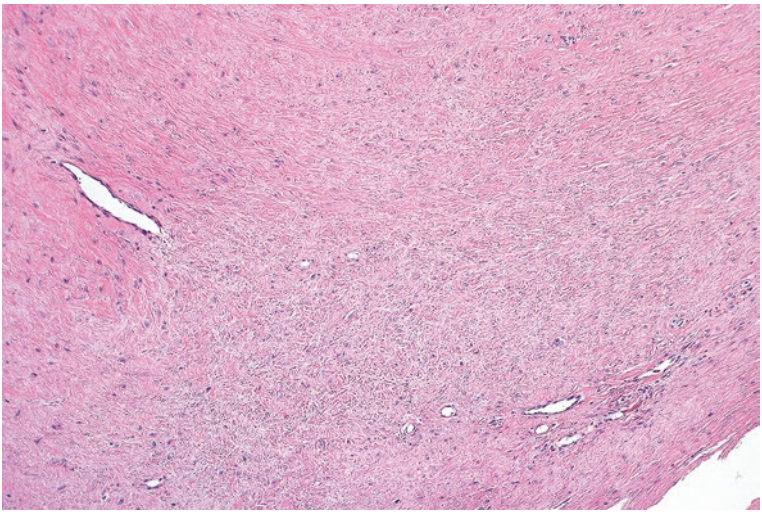

Fig. 5.5 Compressed vascular spaces at the periphery of a fibroma of tendon sheath

Differential Diagnosis

- Nodular fasciitis
- Giant cell tumor of tendon sheath

Comment

1. Although focal areas of fibroma of tendon sheath can resemble nodular fasciitis, nodular fasciitis only rarely arises in the hands and feet. Furthermore, nodular fasciitis clinically arises more rapidly than fibroma of tendon sheath [11].
2. Giant cell tumor of tendon sheath also arises in the hands and feet and can demonstrate fibrosis in long-standing lesions. However, giant cell tumor of tendon sheath will typically retain at least focal areas of hemorrhage or foamy macrophages.
3. Fibroma of tendon sheath is a benign lesion, but does carry a moderate risk of recurrence (approximately 25%) [8]. Patients with recurrence can be cured with a second excision [12].

5.3 Nuchal-Type Fibroma

Nuchal-type fibromas often arise as subcutaneous masses in adults around the head and neck area. Most measure 1–6 cm in greatest dimension [1]. Despite the designation as "nuchal," approximately a third of these lesions will occur at other anatomic sites. Curiously, many patients (approximately 44%) with nuchal-type fibroma also have diabetes mellitus [13].

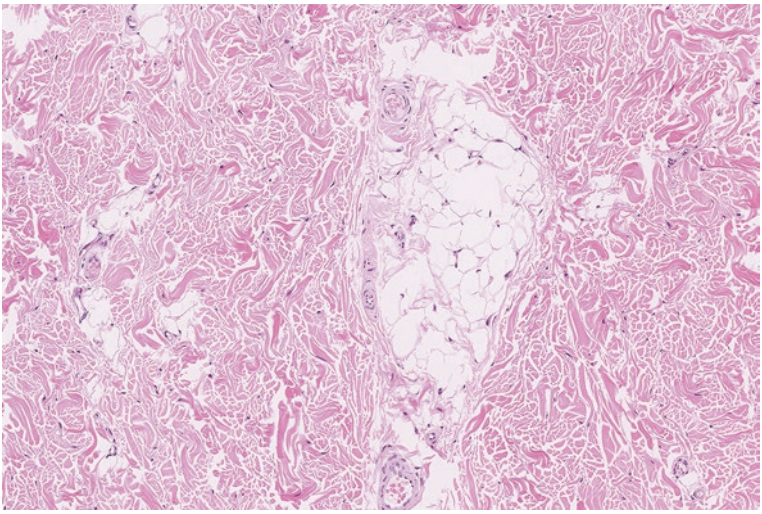

Fig. 5.6 Nuchal-type fibroma with dense ropey collagen and focal area of entrapped adipose tissue

Pathology

Microscopically, these lesions are predominantly composed of dense, ropey collagen with scattered fibroblasts and nests of adipose tissue (Fig. 5.6). This fibrous tissue can entrap focal nerves and adnexal structures [13, 14].

Ancillary Studies

- Ancillary studies are not usually employed for the diagnosis of nuchal-type fibroma. The diagnosis is typically based on the morphologic appearance alone.

Differential Diagnosis

- Elastofibroma
- Gardner-associated fibroma

Comment

1. Elastofibromas also occur in the back or upper neck area. They can be distinguished by the identification of beaded cords of elastin fibers.
2. Nuchal-type fibroma can be difficult if not impossible to distinguish from Gardner-associated fibroma.

3. Consequently, nuchal-type fibroma lesions are often diagnosed as nuchal-type/Gardner-associated fibroma with a comment recommending assessment for clinical features of Gardner syndrome.
4. Lesions with nuchal-type fibroma morphology in children are generally considered to be Gardner-associated fibroma [12].
5. These are benign lesions that are treated with surgical resection. If incompletely excised they can recur.

5.4 Gardner-Associated Fibroma

Gardner-associated fibromas occur in young children and are associated with familial adenomatous polyposis. A timely diagnosis can result in appropriate screening and prevention of future intestinal adenocarcinoma. It often arises as a subcutaneous lesion on the back or head and neck region [15]. In addition to fibromas and intestinal polyposis, patients with Gardner syndrome also present with epidermal inclusion cysts, osteomas, and deep fibromatosis (desmoid tumors) [16].

Pathology
On gross examination, Gardner-associated fibroma appears as a fibrous lesion that can measure up to 12 cm in size. Microscopically, these tumors contain ropey, densely collagenized fibrous tissue with some associated mature adipose tissue (Fig. 5.7). Only focal entrapment of nerves is seen.

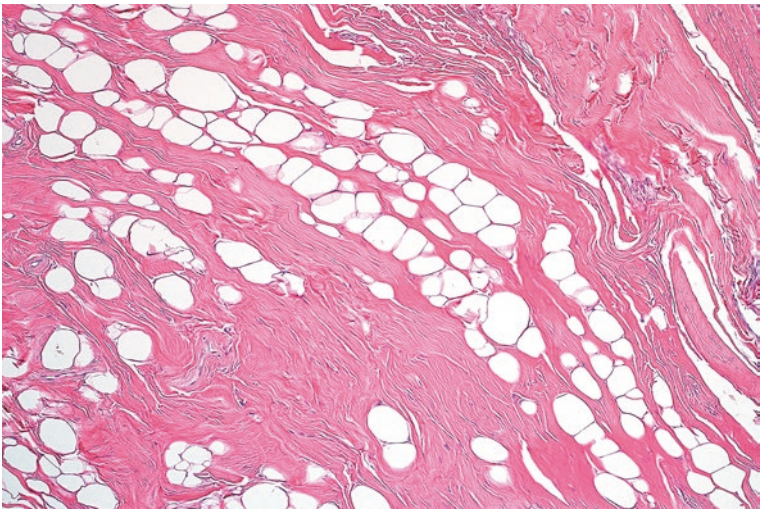

Fig. 5.7 Gardner-associated fibroma with ropey collagen. The appearance is very similar to nuchal-type fibroma

Ancillary Studies

- Gardner-associated fibromas are typically diagnosed based on their morphologic appearance.
- Beta-catenin immunohistochemistry alone is neither sufficiently sensitive nor specific for definitive exclusion or confirmation of the diagnosis [17].

Differential Diagnosis

- Deep fibromatosis (desmoid tumor)
- Nuchal type fibroma

Comment

1. Deep fibromatosis is a fibrotic lesion that can also arise in patients with Gardner syndrome. These neoplasms typically have a more organized arrangement of fibroblasts in a streaming and fascicular architecture.
2. Differentiation between Gardner-associated fibroma and nuchal-type fibroma can be virtually impossible at times. Sometimes, the diagnosis of "nuchal-type/Gardner-associated fibroma" is rendered.
3. Gardner-associated fibromas are treated surgically and may recur if not completely resected.
4. Arranging appropriate screening for other manifestations of Gardner syndrome, such as familial adenomatous polyposis, is key in preventing later onset of a colonic adenocarcinoma [1].

5.5 Elastofibroma

Elastofibroma is a benign fibrous proliferation that usually occurs beneath the muscles around the scapula or chest wall. This lesion predominantly manifests in older adults in the 6th to 7th decade. It is more common in females, and approximately half of patients have bilateral lesions [10, 18].

Pathology
Microscopically, these lesions are primarily composed of fibrous tissue admixed with adipose tissue (Fig. 5.8). On closer examination the fibrous tissue contains vaguely refractive globules and beads of elastin fibers (Fig. 5.9).

Ancillary Studies

- A special stain (Verhoeff elastin stain) will also highlight elastin fibers.

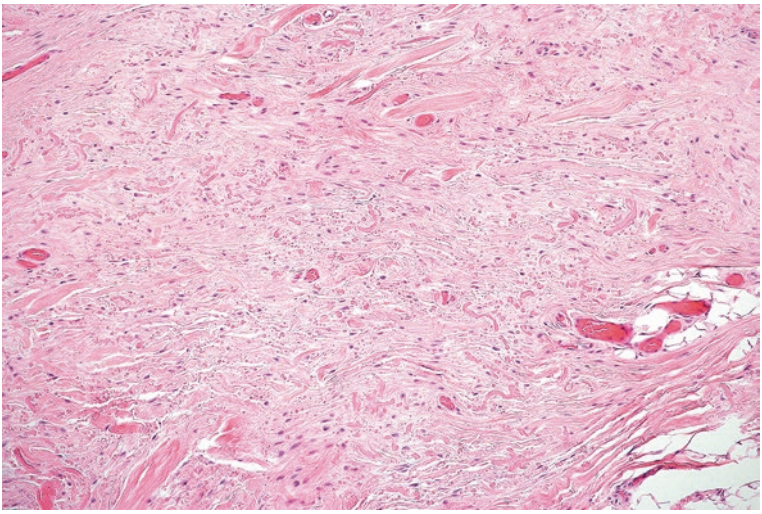

Fig. 5.8 Elastofibroma appears as a fibrotic lesion at low power

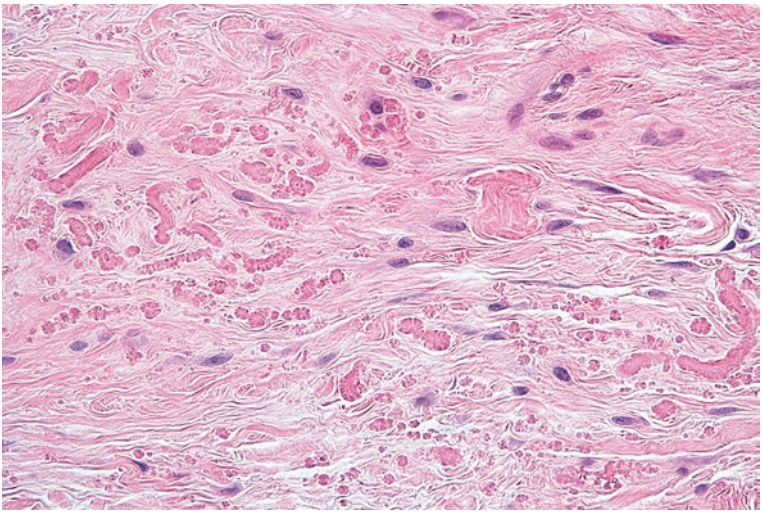

Fig. 5.9 High-power examination of an elastofibroma shows beaded elastin fibers

Differential Diagnosis

- Gardner-associated or nuchal-type fibroma
- Spindle cell lipoma

Comment

1. The extensive amount of fibrous tissue intermixed with adipose tissue can suggest entities such as nuchal-type fibroma or spindle cell lipoma.

2. High-power examination of the H&E slide will typically reveal elastin fibers.
3. Knowledge of the site of origin (beneath the scapula or chest wall) can trigger the pathologist to closely assess for these features.
4. These are benign lesions that can be treated with conservative excision. Recurrence is rare.

5.6 Superficial Fibromatosis

Superficial fibromatosis is a benign proliferation of fibroblasts that can occur in the hand (palmar fibromatosis), foot (plantar fibromatosis), or penis (penile fibromatosis/Peyronie disease). Palmar fibromatosis predominantly occurs in Caucasian men over 65 years. These lesions arise slowly and evolve to the point of causing flexion contractures [1]. Plantar fibromatosis has a broader age distribution and can be found in young adults [19]. Both have been associated with numerous medical conditions such as type I and II diabetes mellitus and alcoholism [20, 21].

Pathology
Superficial fibromatosis grossly appears as fibrous nodules that are typically less than 1 cm in size. Microscopically, they are composed of long bundles of fibroblasts with varying amounts of associated collagen material (Fig. 5.10). Although these can be cellular, there is minimal mitosis or atypical nuclei.

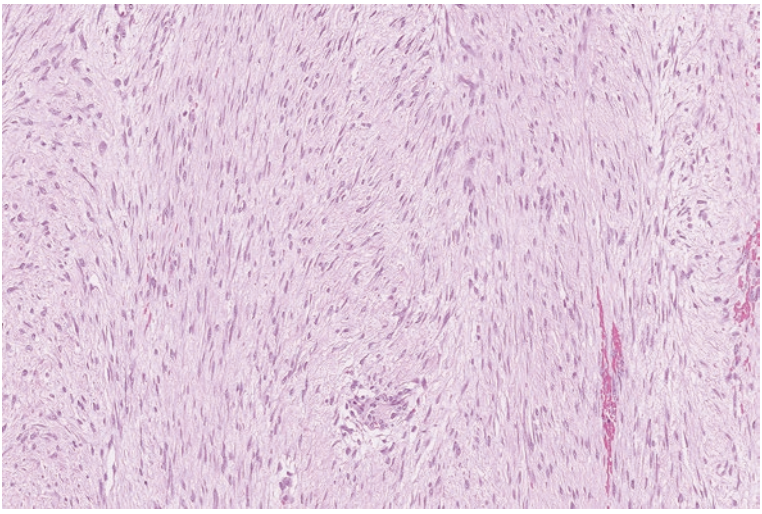

Fig. 5.10 Superficial fibromatosis with long fascicles of spindle cells in the background of fibrous tissue

Ancillary Studies

- A percentage of superficial fibromatosis lesions (approximately 60%) will show nuclear staining for beta-catenin [17].

Differential Diagnosis

- Malignant peripheral nerve sheath tumor
- Synovial sarcoma

Comment

1. While the architecture and cellularity of superficial fibromatosis can mimic more aggressive soft tissue tumors, fibromatosis lacks the nuclear atypia or increased mitoses found in malignant peripheral nerve sheath tumor or synovial sarcoma.
2. Although benign, these lesions frequently recur.
3. Fasciectomy/aponeurosectomy is a common treatment approach [1, 12].

5.7 Deep (Desmoid-Type) Fibromatosis

Deep or desmoid-type fibromatosis is a fibrous proliferation thought to arise from the connective tissue of muscle, overlying fascia, or aponeurosis. Conceptually, these tumors are divided into tumors that arise in the abdominal wall (abdominal fibromatosis), within the abdomen (intra-abdominal fibromatosis), or outside the abdomen (extra-abdominal fibromatosis). Abdominal fibromatosis is usually seen in young women after childbirth [22]. Extra-abdominal fibromatosis often occurs in young adults (median age of 37 years) and arises in the shoulder, spine, thorax, hip, or thigh [23]. Intra-abdominal fibromatosis also occurs in young adults (average age of 41 years). A small subset of these arises as a manifestation of Gardner syndrome, a familial condition that includes deep fibromatosis, Gardner-associated fibroma, and familial adenomatous polyposis [24].

Pathology
Grossly, these tumors have a fibrotic appearance. The microscopic sections show long bundles of bland-appearing fibroblasts that are typically less cellular than superficial fibromatosis. There are varying amounts of background collagenous and myxoid stroma (Fig. 5.11). Occasional prominent capillaries are lodged in between the fascicles and focal extravasated erythrocytes can be seen (Fig. 5.12) [10].

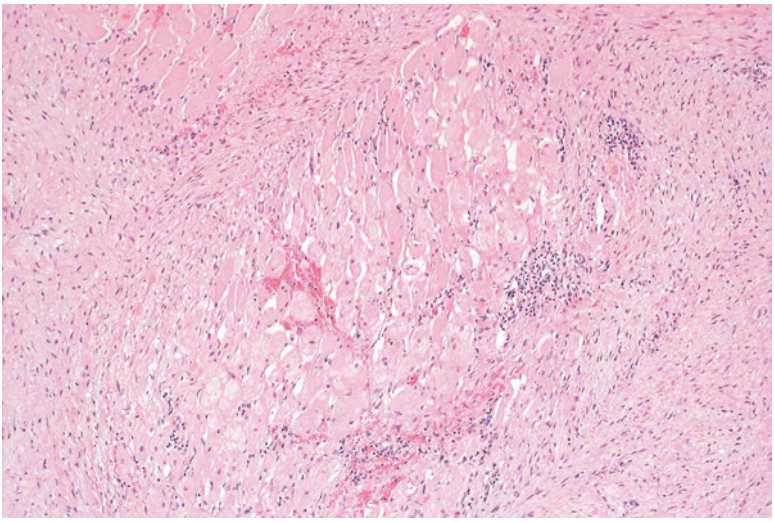

Fig. 5.11 Deep fibromatosis infiltrating around skeletal muscle fibers

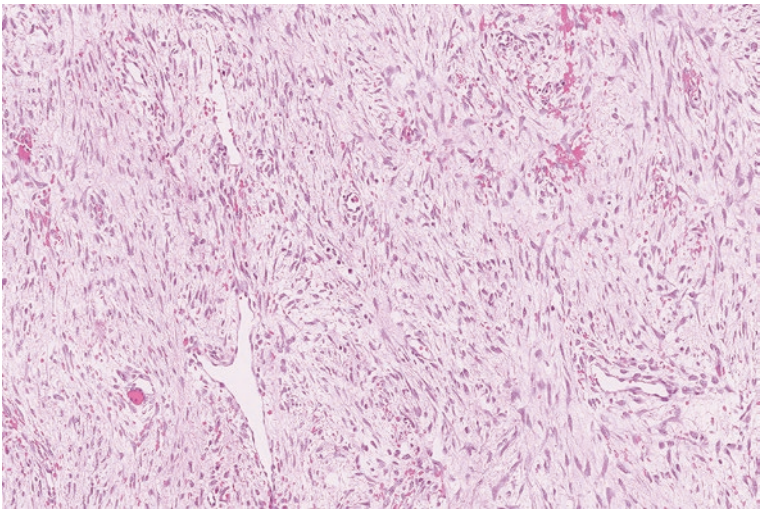

Fig. 5.12 Lodged capillaries and extravasated red blood cells in deep fibromatosis

Ancillary Studies

- Deep fibromatosis is primarily a histologic diagnosis.
- Occasionally, a positive beta-catenin stain or finding of a *CTNNB1* mutation can help confirm the diagnosis [25].

Differential Diagnosis

- Nodular fasciitis
- Retroperitoneal fibrosis
- Gastrointestinal stromal tumor

Comment

1. Deep fibromatosis can focally demonstrate areas of disorganized spindle cells, reminiscent of nodular fasciitis; however, nodular fasciitis typically presents as a more circumscribed lesion in the subcutaneous tissue.
2. Retroperitoneal fibrosis usually presents as a perivascular mass in the abdomen and often contains aggregates of plasma cells that are sometimes positive for IgG4.
3. CD117 and DOG1 immunohistochemical stains are positive in a gastrointestinal stromal tumor and negative in deep fibromatosis.
4. Although deep fibromatosis does not metastasize, it can be locally aggressive.
5. The particular clinical behavior of a deep fibromatosis depends on the site of occurrence.
6. Extra-abdominal deep fibromatosis has a recurrence rate of approximately 35–65%, while abdominal lesions have a recurrence rate of 15–30%.
7. Sporadic intra-abdominal lesions have a low rate of recurrence (12%), while those associated with Gardner syndrome almost always recur (90%) [1].
8. Treatment options include observation. If the lesion is symptomatic or is endangering vital structures, surgical resection can be pursued, though excised lesions can recur. Other treatment options include tamoxifen, non-steroidal anti-inflammatory drugs (NSAIDS), and chemotherapy regimens [26].

5.8 Solitary Fibrous Tumor

Solitary fibrous tumor is a fibroblastic neoplasm that can arise in multiple locations, including the extremities, pelvis, retroperitoneum, pleura, chest wall, and abdominal serosa. These tumors arise in patients of all ages with most extrathoracic lesions occurring in the sixth decade [27]. Rarely, these tumors can induce hypoglycemia, sweating, or even coma by secretion of insulin growth factor [28].

Pathology
Grossly, these neoplasms are fibrotic but can exhibit cystic degeneration. Under the microscope, solitary fibrous tumors are said to demonstrate a “patternless pattern”, which refers to the highly variable appearances that a pathologist can encounter in a single tumor. In more cellular portions of a solitary fibrous tumor, ovoid to spindle cells are arranged around branching vessels of varying shapes and sizes (Fig. 5.13). In less cellular portions, there are scattered ovoid cells in the background of dense collagen and vessels with perivascular hyalinization (Figs. 5.14 and 5.15).

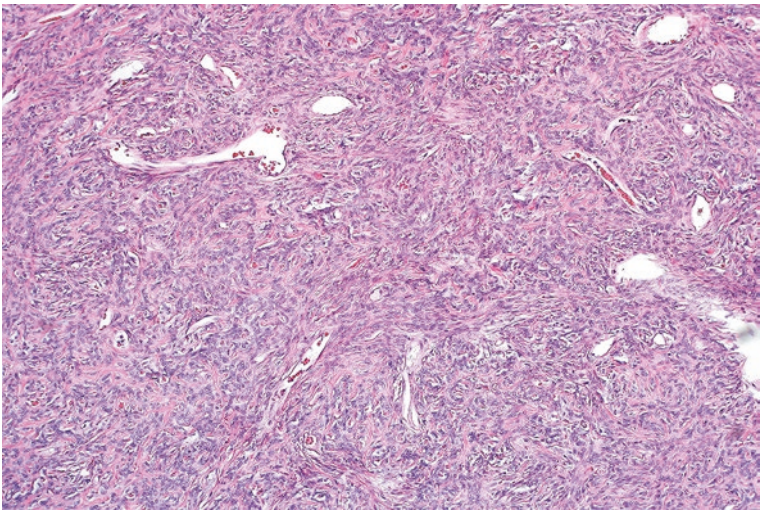

Fig. 5.13 Cellular solitary fibrous tumor with a dense population of ovoid tumor cells

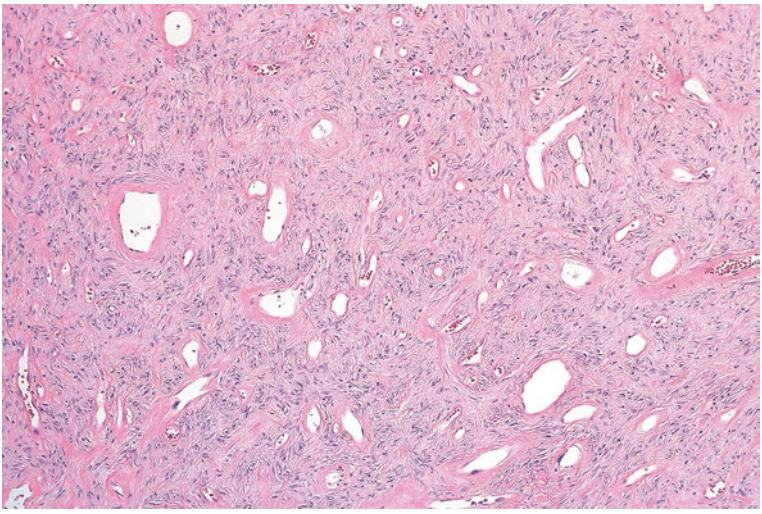

Fig. 5.14 Scattered vascular spaces in a less cellular area of solitary fibrous tumor

Ancillary Studies

- Solitary fibrous tumor is often positive for CD34 and bcl-2 immunohistochemical stains [29].
- Recently, solitary fibrous tumor has been found to have a unique translocation between the *NAB2* and *STAT6* genes.
- Positive nuclear staining with a STAT6 immunohistochemical stain is fairly specific for solitary fibrous tumor [30].

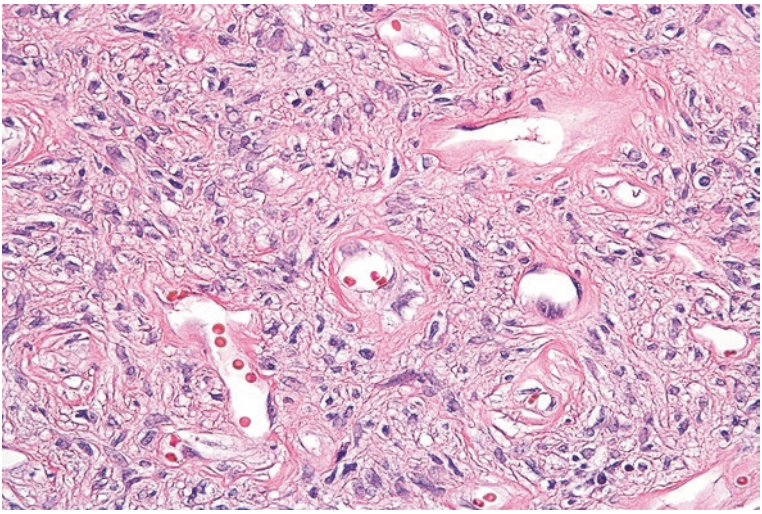

Fig. 5.15 Solitary fibrous tumor with bland ovoid cells in a background of fibrosis

Differential Diagnosis

- Synovial sarcoma
- Schwannoma
- Spindle cell lipoma

Comments

1. Given its highly variable morphologic appearance, solitary fibrous tumor has a broad differential diagnosis.
2. Synovial sarcoma can have spindle cells and branching vessels, but is usually negative for CD34.
3. Schwannomas with degenerative changes can exhibit the perivascular hyalinization seen in solitary fibrous tumor. Unlike schwannomas, solitary fibrous tumors are negative for S100.
4. Both spindle cell lipomas and solitary fibrous tumors are positive for CD34; however, spindle cell lipoma will not stain for STAT6.
5. Since solitary fibrous tumors can metastasize, these are overall considered to be intermediate in behavior. However, predicting which tumors will result in metastasis has been problematic.
6. A recently published stratification model utilizes age, size, and mitosis to calculate risk for metastasis and disease free survival.

7. Using this algorithm, tumors considered low-risk have no risk for metastasis and no disease-specific mortality. Patients with intermediate-risk have a 10-year metastasis-free and disease-specific survival rates of 64% and 93%, respectively. High-risk lesions inevitably result in metastasis and disease-specific mortality after 10 years [31].
8. Complete excision is the standard treatment for solitary fibrous tumors.

5.9 Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor is a soft tissue neoplasm that often arises in children and young adults in the abdomen, pelvis, or retroperitoneum [32]. Patients with these tumors can rarely present with constitutional symptoms of fever or weight loss, increased erythrocyte sedimentation rate, thrombocytosis, or microcytic anemia [33].

Pathology
Microscopically, these neoplasms are composed of haphazardly arranged bland-appearing spindle cells and an associated inflammatory cell population (Fig. 5.16). Other areas of inflammatory myofibroblastic tumors can be less cellular and demonstrate increased collagen deposition (Fig. 5.17) [32].

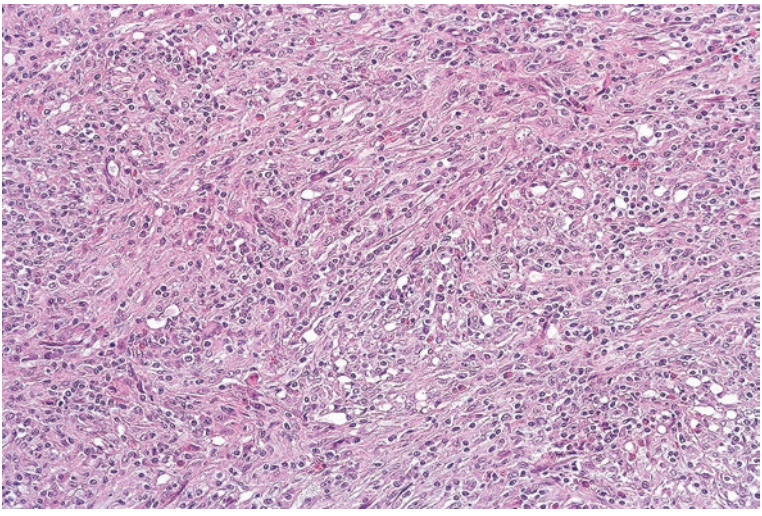

Fig. 5.16 Inflammatory myofibroblastic tumor with a haphazard arrangement of spindle cells and associated chronic inflammation

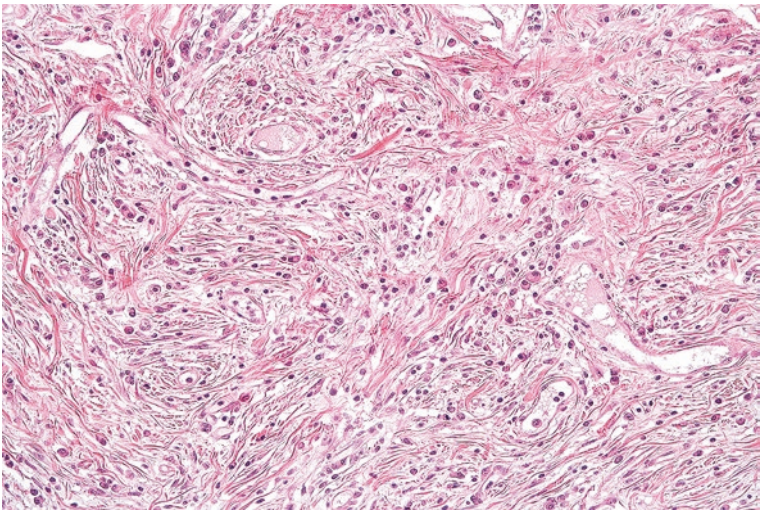

Fig. 5.17 Long-standing inflammatory myofibroblastic tumor with extensive collagen deposition

Ancillary Studies

- Fifty percent of inflammatory myofibroblastic tumors are positive for ALK immunohistochemical stain and demonstrate clonal rearrangements involving the *ALK* gene (2p23).

Differential Diagnosis

- Gastrointestinal stromal tumor
- Dedifferentiated liposarcoma
- Desmoid fibromatosis

Comments

1. Inflammatory myofibroblastic tumor arising in the abdomen can be mistaken for gastrointestinal stromal tumor. However, inflammatory myofibroblastic tumors are negative for a CD117 immunohistochemical stain.
2. Dedifferentiated liposarcomas also arise in the abdomen and can have associated inflammation. If this diagnosis is in question, FISH studies will show inflammatory myofibroblastic tumor to be negative for the *MDM2* gene amplification found in well-differentiated and dedifferentiated liposarcoma.
3. Desmoid fibromatosis can have focal areas of disorganization, but examination of other parts of the tumor will reveal a more organized fascicular pattern of spindle cells.

4. Although inflammatory myofibroblastic tumors often recur, incidence of metastasis is less than 5%. A rare variant of inflammatory myofibroblastic tumor with a more epithelioid morphology behaves in a more agressive fashion [34].
5. Surgical resection is the primary treatment. Adjuvant radiation or chemotherapy is sometimes administered for recurrent lesions. Crizotinib, an ALK inhibitor, can prove helpful for adjuvant treatment.

5.10 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a neoplasm that typically arises in young adults, with the peak incidence occurring in the third decade of life. Clinically, this begins as a plaque-like thickening of the skin and steadily progresses to a subcutaneous nodular mass over the course of several years. Frequent sites of involvement include the trunk and proximal upper and lower extremities [35].

Pathology
Grossly, these are typically solitary masses that are multinodular and measure several centimeters in size (average of 5.0 cm). Although these are highly infiltrative tumors, they can appear deceivingly well circumscribed to the naked eye [35]. Microscopically, dermatofibrosarcoma protuberans is composed of bland-appearing spindled fibroblasts that are arranged in an irregularly whorled or storiform pattern (Fig. 5.18). The tumor is notorious for percolating into underlying subcutaneous adipose tissue (Fig. 5.19) [36]. Additionally, the cells extend along connective tissue septa, making resection particularly difficult (Fig. 5.20).

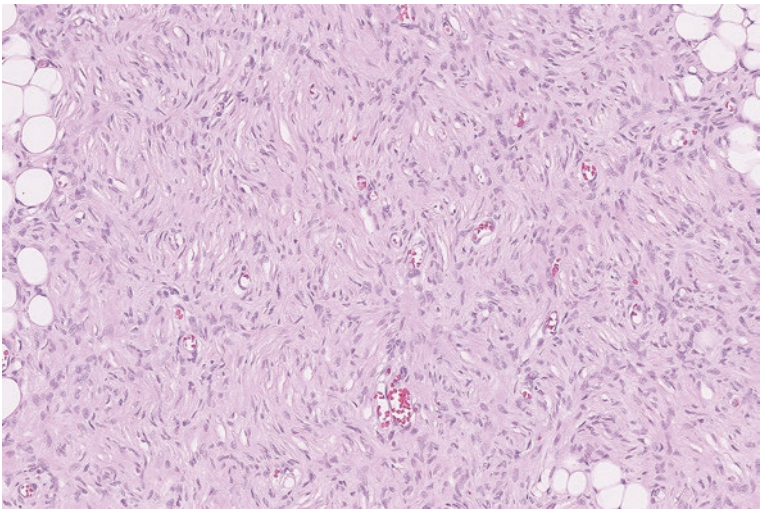

Fig. 5.18 Dermatofibrosarcoma protuberans with a whorled, storiform pattern

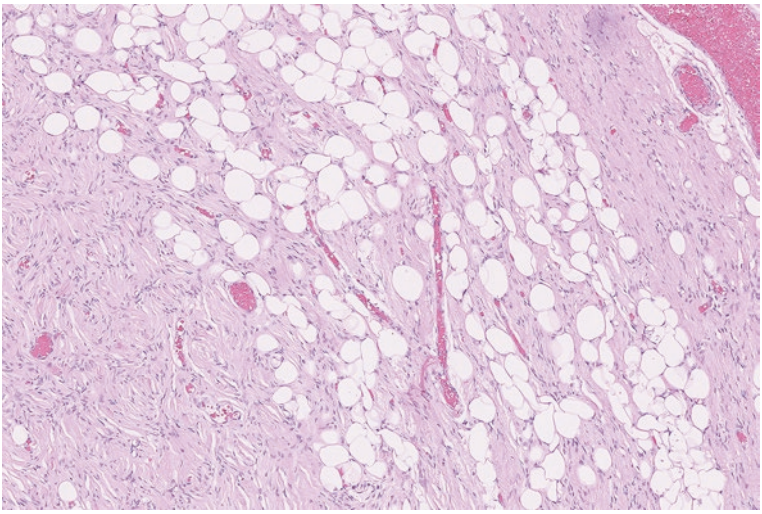

Fig. 5.19 Dermatofibrosarcoma protuberans entrapping the underlying adipocytes of the subcutaneous tissue

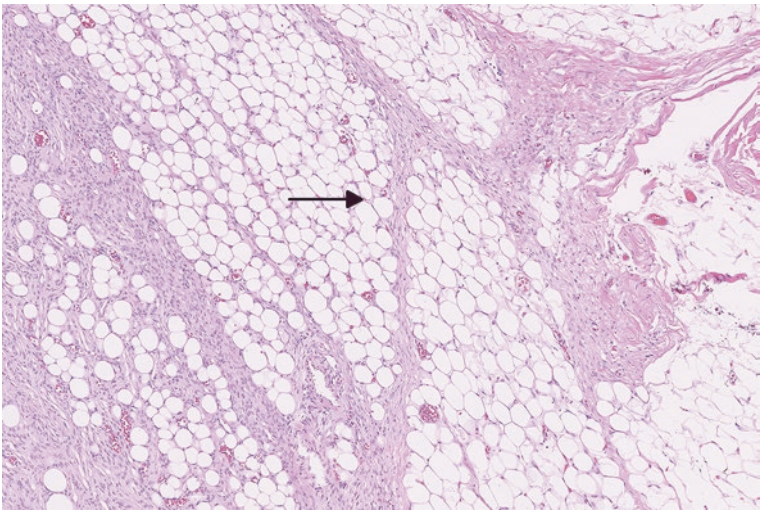

Fig. 5.20 Dermatofibrosarcoma protuberans extending long tentacles into the surrounding adipose tissue (*arrow*)

Occasionally, a DFSP can have a more aggressive component where the spindle cells organize in a bundled or fascicular arrangement (Fig. 5.21). This variant is referred to as the fibrosarcomatous variant of dermatofibrosarcoma protuberans [37].

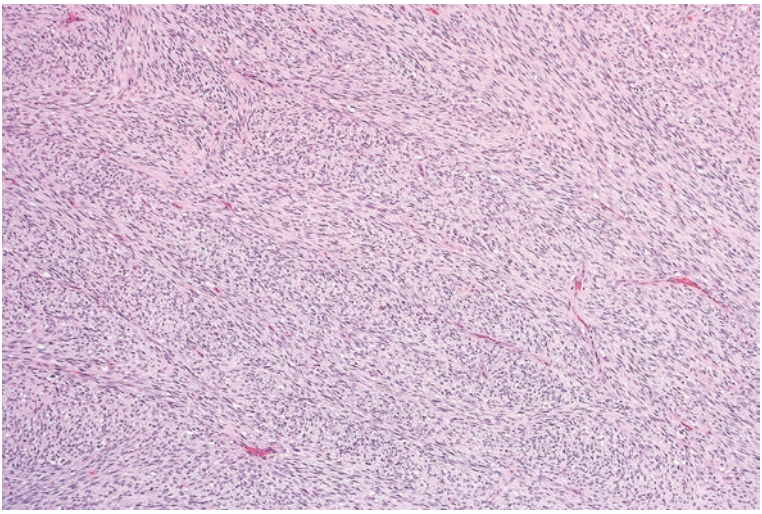

Fig. 5.21 Fibrosarcomatous variant of dermatofibrosarcoma protuberans. The cells have a more organized and bundled arrangement

Ancillary Studies

- Dermatofibrosarcoma protuberans is strongly positive for a CD34 immunohistochemical stain.
- This neoplasm manifests a unique (and diagnostic) fusion of the *COL1A1* and *PDGFB* genes, which can be detected by FISH.

Differential Diagnosis

- Fibrous histiocytoma (dermatofibroma)

Comment

1. Unlike dermatofibrosarcoma protuberans, fibrous histiocytoma tends to be limited to the dermis.
2. Assessment for the *COL1A1-PDGFB* fusion gene can be helpful in difficult cases.
3. Treatment is primarily surgical; however, the infiltrative nature of DFSP can sometimes complicate resection. With only conservative excision, these tumors frequently recur (43%) and rarely metastasize.
4. The generous margins provided by a wide excision reduce recurrence to approximately 18%. Mohs micrographic surgery has an average recurrence rate of 0.6% [38].
5. The fibrosarcomatous variant of DFSP has been associated with higher rates of recurrence (58%) and metastasis (15%) in patients that receive conservative excision [39].

6. However, a fibrosarcomatous variant of DFSP that is completely resected by wide excision behaves similarly to conventional DFSP, with almost no reported metastasis [37].

5.11 Congenital/Infantile Fibrosarcoma

Congenital/infantile fibrosarcoma is a fibroblastic neoplasm that almost always arises in the first year of life. In fact, approximately a third of these tumors will be present at the time of birth. Frequent sites of involvement include the superficial and deep soft tissues of the extremities, trunk, and head and neck. These lesions can measure up to 20 cm in greatest dimension [40, 41].

Pathology

Grossly, infantile fibrosarcoma appears as a poorly circumscribed fleshy mass that can contain hemorrhage or necrosis. The microscopic sections show highly cellular intersecting bundles of ovoid to spindle cells (Fig. 5.22). Substantial mitoses, chronic inflammation, or necrosis can be present (Fig. 5.23). Varying amounts of associated branching vessels and hyalinized fibrosis can be seen [9].

Ancillary Studies

- Infantile fibrosarcoma exhibits a t(12;15) chromosomal translocation which results in the formation of an *ETV6-NTRK3* fusion transcript [42].
- This fusion transcript can also be found in many other malignancies including congenital mesoblastic nephroma, acute myeloid leukemia, secretory carcinoma of the breast, and radiation association papillary thyroid carcinoma [43].

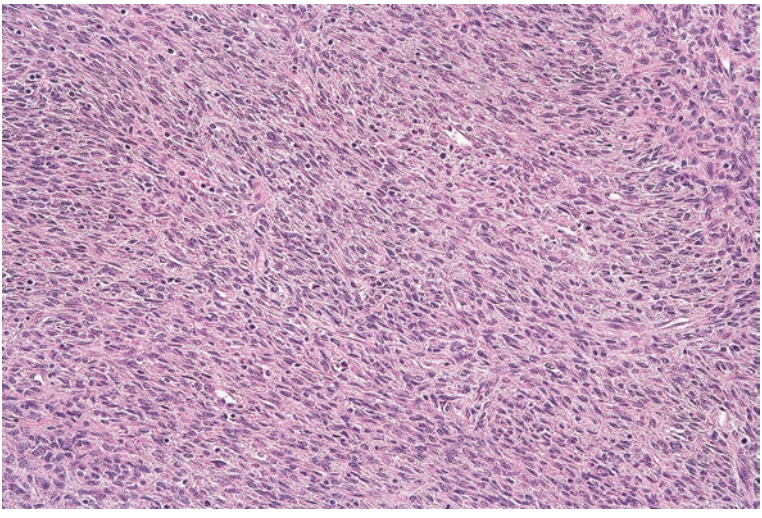

Fig. 5.22 Infantile fibrosarcoma with intersecting bundles of spindle cells arranged in a fascicular pattern

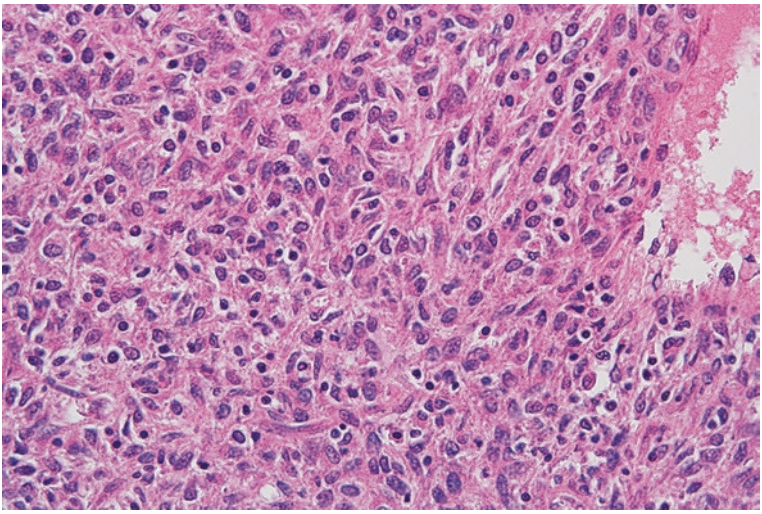

Fig. 5.23 Infantile fibrosarcoma with elongated nuclei showing scattered mitoses

Differential Diagnosis

- Spindle cell rhabdomyosarcoma
- Infantile fibromatosis

Comment

- Although spindle cell rhabdomyosarcoma occurs in young patients and can demonstrate a fascicular pattern, these tumors will be positive for desmin and MyoD1 immunohistochemical stains.
- Congenital/infantile fibrosarcoma is typically more organized and has higher cellularity than fibromatosis. The finding of an *ETV6-NTRK3* fusion transcript distinguishes infantile fibrosarcoma from fibromatosis.
- Despite its intimidating appearance, infantile fibrosarcoma only occasionally (17%) recurs and rarely metastasizes. The 5-year survival is 84% [1, 9].
- Wide local excision is the primary treatment for congenital/infantile fibrosarcoma.

5.12 Low-Grade Fibromyxoid Sarcoma

Low-grade fibromyxoid sarcoma is a malignancy that often arises in the deep soft tissue of the trunk and extremities. These tumors occur over a broad age range (median age of 34 years), and pediatric patients are occasionally affected. Typically, low-grade fibromyxoid sarcoma arises as a slowly growing mass that eventually reaches an average size of 8–10 cm [1, 44].

Pathology

On gross examination these tumors appear well circumscribed. Microscopically, they are composed of bland-appearing fibroblasts embedded in variably myxomatous and collagenous stroma (Figs. 5.24 and 5.25). A delicate branching capillary network is present (Fig. 5.26) [45].

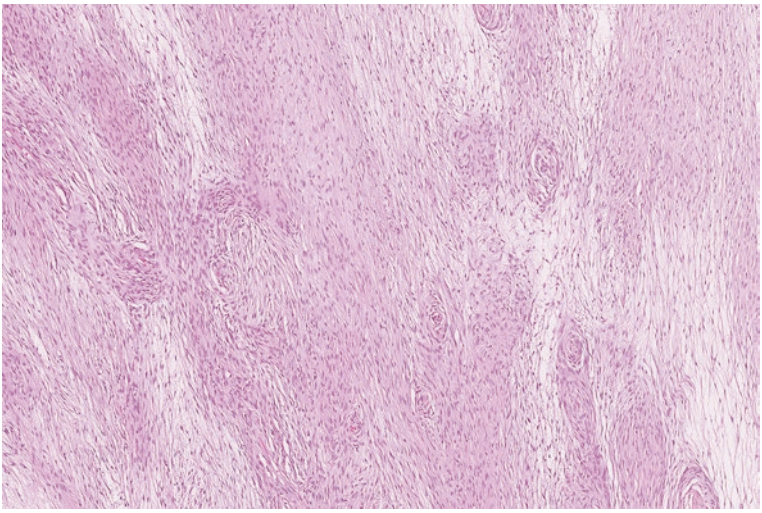

Fig. 5.24 Low-grade fibromyxoid sarcoma with an alternating hyalinized and myxoid background

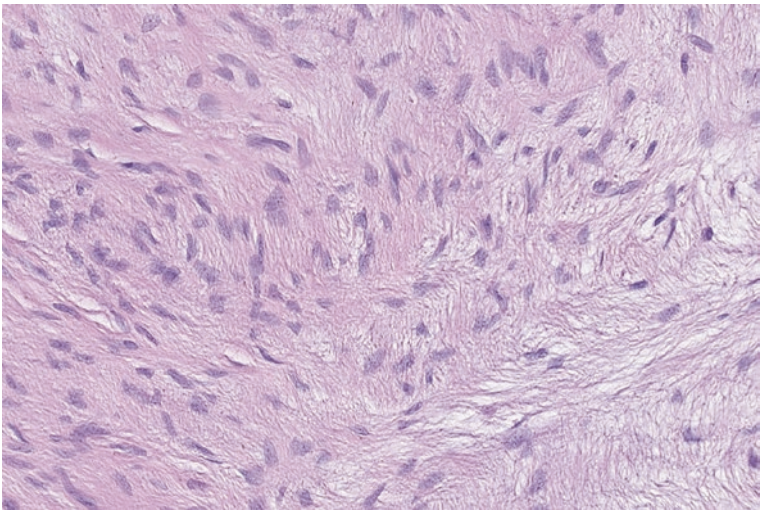

Fig. 5.25 Fibroblastic cells of low-grade fibromyxoid sarcoma are deceivingly bland in appearance

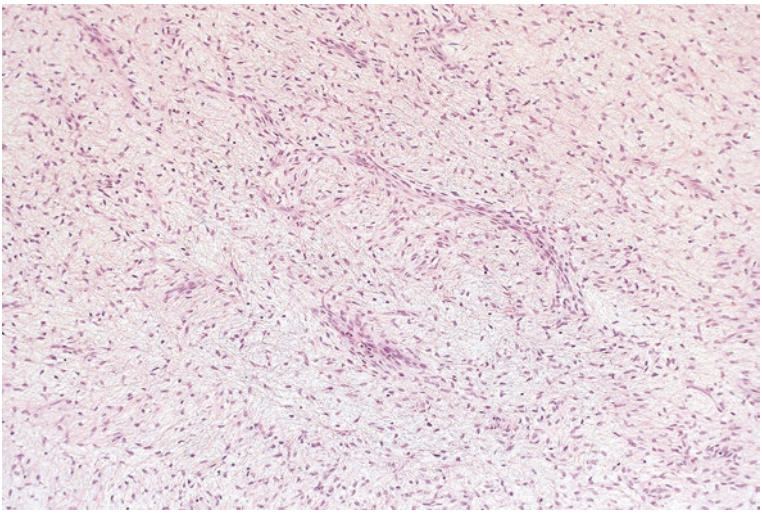

Fig. 5.26 Delicate branching network of low-grade fibromyxoid sarcoma

Ancillary Studies

- A MUC4 immunohistochemical stain is positive in low-grade fibromyxoid sarcoma [46].
- This tumor has a unique translocation of t(7;16) that results in a *FUS-CREB3L2* fusion transcript [47].
- Rare tumors will exhibit a variant t(11;16) translocation that produces a *FUS-CREB3L1* fusion transcript [48].

Differential Diagnosis

- Myxofibrosarcoma
- Perineurioma
- Deep fibromatosis

Comment

- Tumor cells in myxofibrosarcoma exhibit more nuclear atypia and hyperchromasia than seen in low-grade fibromyxoid sarcoma.
- The deceivingly bland appearance of the cells in low-grade fibromyxosarcoma often causes it to be mistaken for less aggressive lesions such as deep fibromatosis or a perineurioma.
- The finding of a positive MUC4 stain or *FUS-CREB3L2* fusion transcipt helps differentiate low-grade fibromyxoid sarcoma from alternative diagnoses.
- Although low-grade fibromyxoid sarcoma is clinically indolent in the short term, recurrence and metastasis can occur decades after resection of the primary lesion.

- In a study with long-term follow-up, 64% of patients had local recurrence and 45% of patients experienced metastasis [49].
- Standard treatment consists of wide excision and close clinical follow-up.

5.13 Myxofibrosarcoma

Myxofibrosarcoma frequently manifests in the proximal extremities of adults with a peak incidence in the seventh decade of life [50]. These tumors are often relatively superficial, with two thirds arising in the dermis or subcutaneous tissue [51]. Although myxofibrosarcomas clinically have a nodular appearance, they are particularly infiltrative in nature and generous margins are often taken to ensure complete resection.

Pathology

The tumor grossly demonstrates a mucoid appearance. Histologically, myxofibrosarcomas contain myxoid material that surrounds a conspicuous network of curved vessels and mesenchymal cells with nuclear hyperchromasia (Figs. 5.27 and 5.28). Occasional cells can have a vacuolated cytoplasm that mimics immature fat cells. In higher-grade tumors, the neoplastic cells are more prevalent and aggregate in a clustered or sheet-like arrangement (Fig. 5.29). In the past, these high-grade myxofibrosarcomas have been referred to as "myxoid malignant fibrous histiocytoma" [51, 52].

Ancillary Studies

- Immunohistochemical stains or genetics studies are not particularly helpful in confirming the diagnosis.

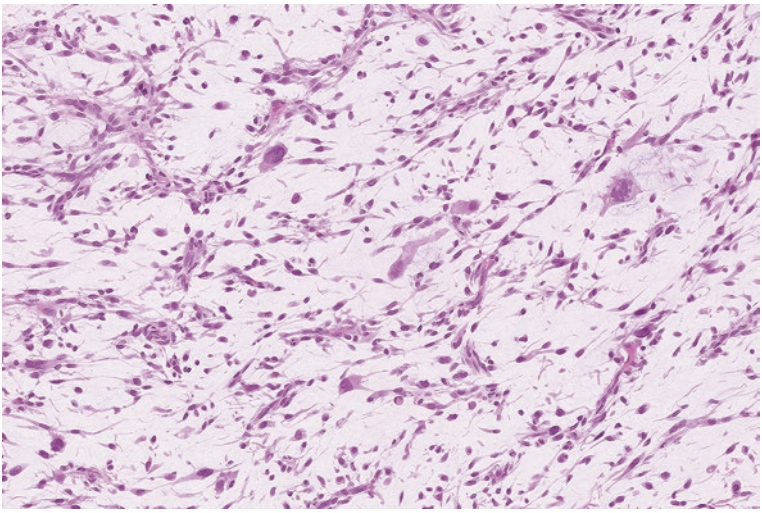

Fig. 5.27 Myxofibrosarcoma with myxoid background and curvilinear vessels

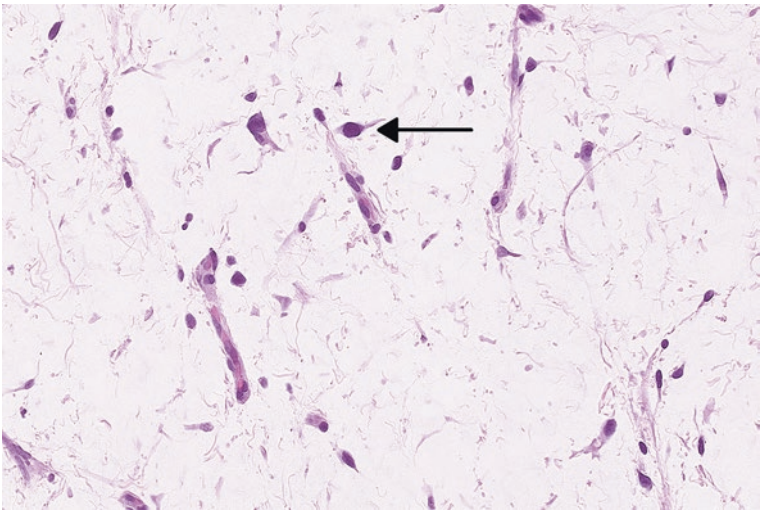

Fig. 5.28 Cells containing enlarged, hyperchromatic, and highly atypical nuclei in a myxofibrosarcoma (*arrow*)

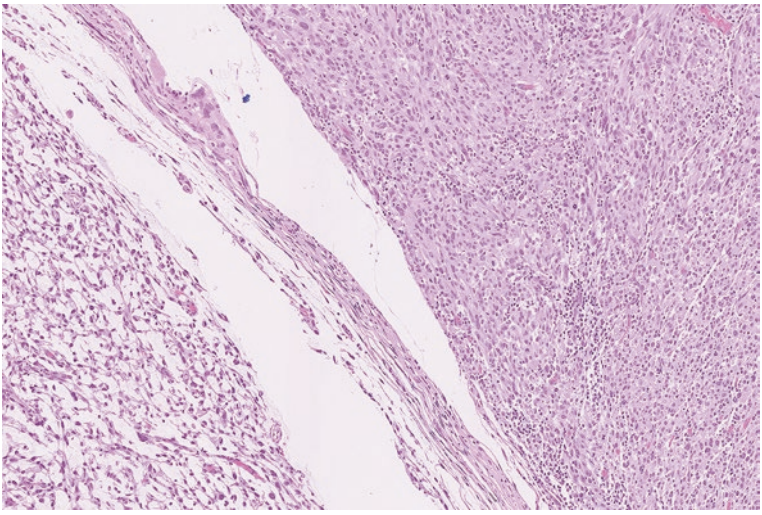

Fig. 5.29 Transition to high-grade myxofibrosarcoma. The high-grade component demonstrates sheets of anaplastic tumor cells with little to no myxoid background

Differential Diagnosis

- Low-grade fibromyxoid sarcoma
- Myxoid liposarcoma
- Intramuscular myxoma

Comment

- Myxofibrosarcoma contains cells with nuclear atypia and hyperchromasia that are not usually seen in myxoma, low-grade fibromyxoid sarcoma, or myxoid liposarcoma.
- Myxofibrosarcomas frequently recur with an overall rate of recurrence of 50–60% [12].
- The metastatic potential of these tumors is highly dependent on the histologic grade. The overall metastatic rate of myxofibrosarcoma is 35%, but grade 1 tumors were found not to metastasize [53].
- Tumors measuring greater than 5 cm or containing less than 75% myxoid component or necrosis, are at increased risk for disease-specific mortality [54].
- Complete surgical excision with a clear margin of at least 2 cm or an intact anatomic barrier is the primary treatment for myxofibrosarcoma. If the margins are involved or close, then adjuvant radiation therapy can be administered [12].

5.14 Adult-Type Fibrosarcoma

Several decades ago, adult-type fibrosarcoma was one of the most frequently diagnosed soft tissue sarcomas; however, pathologists have since recognized that other soft tissue neoplasms can manifest a fibrosarcoma-like morphology, such as fibrosarcomatous variant of dermatofibrosarcoma protuberans. As classification has become much more detailed, the diagnosis of adult fibrosarcoma has become increasingly rare [55]. These tumors often present as a deep mass in the lower extremities in association with the fascia or skeletal muscle. They typically occur in older adults [56].

Pathology
Adult-type fibrosarcomas are composed of organized intersecting bundles of spindle cells with nuclear hyperchromasia and some associated collagen (Fig. 5.30). Importantly, other features of more specific variants of fibrosarcoma (e.g., myxofibrosarcoma, fibromyxoid sarcoma) are not present [55].

Differential Diagnosis

- Low-grade fibromyxoid sarcoma or myxofibrosarcoma
- Deep fibromatosis
- Malignant peripheral nerve sheath tumor
- Monophasic synovial sarcoma
- Fibrosarcomatous variant of dermatofibrosarcoma protuberans
- Undifferentiated pleomorphic sarcoma

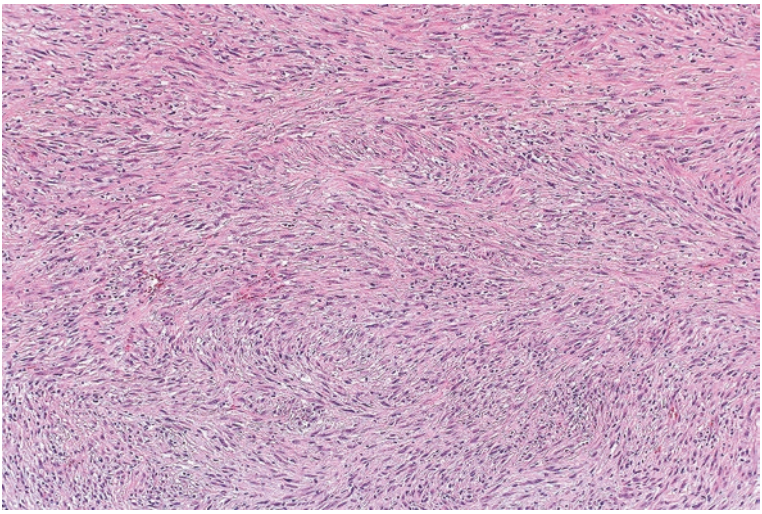

Fig. 5.30 Spindle cells arranged in a fascicular architecture in an adult-type fibrosarcoma

Comment

- A diagnosis of adult-type fibrosarcoma should be made only after all other possibilities have been excluded.
- Careful examination and appropriate cytogenetic studies and immunohistochemical stains are needed to consider these alternatives [10].
- Fifty percent of patients die from recurrent or metastatic disease [55].

Facts to Remember

1. Nodular fasciitis is a benign lesion that can be clinically concerning due to its initial rapid enlargement.
2. Recognition of Gardner-associated fibroma is critical as this can initiate timely screening for familial adenomatous polyposis.
3. Although not metastatic, deep fibromatosis is a locally aggressive soft tissue neoplasm that can infiltrate vital structures. Recurrence can occur, particularly in patients with Gardner syndrome.
4. Solitary fibrous tumor is a fibrous neoplasm which can arise in numerous locations and can metastasize. Risk factors for metastasis include older age, size of tumor, and mitosis.
5. Dermatofibrosarcoma protuberans is a highly infiltrative lesion that can recur and rarely metastasize. However, wide excision with generous margins is often curative.
6. Low-grade fibromyxoid sarcoma is a deceivingly bland appearing lesion under the microscope, but is capable of metastasis many years after diagnosis. Close clinical follow-up is warranted.

7. Myxofibrosarcoma is a soft tissue sarcoma that usually arises in the subcutaneous tissue of older adults. Approximately a third of these tumors metastasize.
8. Adult-type fibrosarcoma is now a rare entity. Diagnosis should only be made when other possibilities are excluded.

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