4 Benign Fibrous, Fibrohistiocytic, and Myofibroblastic Lesions

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Abstract

This chapter covers a large number of benign entities grouped together for convenience under the broad categories of fibrous, fibrohistiocytic, and myofibroblastic lesions. Fibrous lesions generally demonstrate a conspicuous increase in collagen production and varying numbers of fibroblastic spindle cells. "Fibrohistiocytic," a somewhat enigmatic term, is a general descriptor for tumors containing a combination of spindle cells of putative fibroblastic, myofibroblastic, and/or primitive mesenchymal cell origin and histiocytes (bone marrow-derived tissue macrophages and dendritic cells). Myofibroblastic lesions are composed of spindle cells with combined features of smooth muscle cells and fibroblasts.

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Keloid

Clinical Features

Keloid is a benign fibrous tumor resulting from an abnormal wound-healing response to cutaneous infection and/or injury in susceptible patients, particularly those of African descent. It often occurs in younger patients, demonstrates a strong familial predisposition, and may be solitary or multifocal. Keloid typically presents as a well-demarcated nodular cutaneous mass, which may have an erythematous appearance. Common sites include the head and neck, especially earlobes, and upper torso, particularly the presternal region. Keloids are benign but frequently recur. Surgery combined with intralesional corticosteroids and cryotherapy is considered first-line treatment.

Pathologic Features

Keloid is a hypocellular dermal-based fibroproliferative lesion comprised of prominent thick, glassy bundles of collagen fibers and admixed bland fibroblasts that extend beyond the point of cutaneous injury (Fig. 4.1). Early lesions show variable numbers of small vessels, while older lesions may contain areas of calcification and/or osseous metaplasia. By immunohistochemistry, the spindled cells are usually at least focally positive for SMA, usually exhibiting a membranous (tram-track) staining pattern typical of myofibro-

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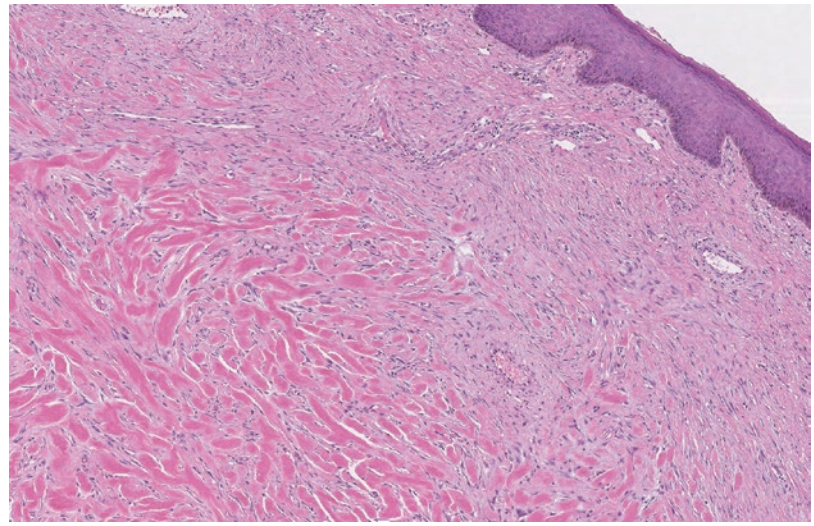


Fig. 4.1 Keloid. A hypocellular dermal-based fibroproliferative lesion composed of prominent, thick glassy eosinophilic collagen bundles admixed with bland fibroblasts

Table 4.1 Key pathologic features: keloid

Hypocellular fibroproliferative lesion
Prominent thick, glassy bundles of collagen admixed with bland fibroblasts
Focal SMA positivity

blasts. HtrA1, a serine protease, may promote keloid development by accelerating cell proliferation and remodeling of keloid-specific extracellular matrix or cell surface molecules (Table 4.1).

Differential Diagnosis

The main differential diagnosis for keloid is hypertrophic scar, although objectively it could be argued that keloid is essentially a form of hypertrophic scar. In contrast to keloid, hypertrophic scars generally are limited to the site of cutaneous injury, contain spindle cells oriented parallel to the overlying epidermis superficially, and do not show prominent thick, glassy bundles of collagen fibers. Older lesions of nodular fasciitis and dermatofibromas may sometimes contain keloidal collagen fibers, but unlike the hypocellular keloid, have cellular areas more typical of those entities.

Fibrous Papule (Angiofibroma)

Clinical Features

Fibrous papule is a member of the broad and diffuse group of superficial angiofibromata that includes the so-called acral angiofibromas (including acral fibrokeratomas, such as acquired digital fibrokeratoma, subungual and periungual Koenen tumors of tuberous sclerosis complex [TSC], and acquired "garlic clove" periungual fibroma), facial angiofibromas of TSC ("adenoma sebaceum"), and pearly penile papules. Only fibrous papule and digital fibrokeratoma (next section) will be discussed at length, as they are the most commonly encountered entities within this group and their key histopathologic features can, to a large degree, be extrapolated to the other lesions with some minor differences. In addition to TSC, angiofibromata have been associated with other syndromes including multiple endocrine neoplasia (MEN) type 1, Birt-Hogg-Dubé syndrome, and Hornstein-Knickenberg syndrome, a phenotypic variant of Birt-Hogg-Dubé syndrome. All are benign lesions cured by simple excision or locally destructive techniques like cryo- or laser therapy. Systemic therapies involving mTOR

inhibitors have shown some utility in treating lesions associated with TSC.

Fibrous papules (FP) are small dome-shaped papules, which usually present on the nose and face of adults. Clinically, a melanocytic lesion, wart, or basal cell carcinoma are usually suspected. A subset of FP is seen in association with tuberous sclerosis, or uncommonly in Birt-Hogg-Dubé syndrome, although most appear to be sporadic.

Pathologic Features

All superficial angiofibromata share certain histopathologic features, including a dome-shaped or papillomatous silhouette, the presence of numerous blood vessels, varying amounts of hyalinized collagen, and spindled-to-stellate-to-multinucleated "fibroblastic" cells.

Classic examples of FP demonstrate a paucicellular proliferation of stellate-shaped fibroblasts within a dense fibrous stroma containing small ectatic vessels (Fig. 4.2a). Occasionally, multinucleated cells may be seen (Fig. 4.2b). A variety of histopathologic subtypes, including hypercellular, clear cell, pigmented, pleomorphic, granular cell, inflammatory, and epithelioid variants, have been described. Hypercellular FP shows a dense infiltrate of round-to-ovoid fibroblasts with a nevoid appearance. Clear cell FP contains a proliferation of round cells with foamy cytoplasm resembling foamy macrophages or epithelial cells with clear cell change (Fig. 4.2c and d). The granular cell variant is similar to the clear cell variant, but with much coarser intracytoplasmic granules (Fig. 4.2e). Pleomorphic FP contains stellate fibroblasts with bizarre pleomorphism similar to those seen in pleomorphic fibroma, discussed below (Fig. 4.2f). Pigmented FP differs only by the presence of melanophages within the lesion (Fig. 4.2g). Inflammatory FP has the addition of a brisk inflammatory infiltrate (Fig. 4.2h). Epithelioid fibrous papule contains epithelioid cells with abundant eosinophilic cytoplasm (Fig. 4.2i). The spindled and stellate cells seen in all variants are positive for FXIIIa and negative for S100 protein. CD34 positivity has been rarely reported. Other nonspecific markers such as CD68 and lysozyme may be positive as well. Clinical and histopathologic features are usually sufficient to make the diagnosis, and immunostains are rarely required, except to rule out entities in the differential diagnosis (Table 4.2).

Differential Diagnosis

Hypercellular FP must be differentiated from a melanocytic lesion with melanocytic markers. Clear cell FP often resembles foamy macrophages, which are diffusely positive for CD163, or epithelial neoplasms such as clear cell squamous cell carcinoma and perhaps metastatic renal cell carcinoma, for which keratins and PAX-8 are useful. Pleomorphic FP should be differentiated from atypical fibroxanthoma and pleomorphic dermal sarcoma, both of which have higher cellularity, greater nuclear atypia, and mitotic activity. Pigmented FP typically demonstrate melanocytic hyperplasia and melanophages, similar to a melanocytic lesion, but the latter are positive for melanocytic markers such as S100 protein, Melan-A, and MITF. Depending on the density of the inflammatory infiltrate seen in an inflammatory FP, one might consider a hematolymphoid neoplasm. However, the infiltrate in FP is polymorphous with small and large lymphocytes, plasma cells, tissue macrophages, and scattered eosinophils and neutrophils. Additionally, the identification of the classic fibrous stroma and ectatic vessels seen in all FP variants, as well as the clinical features, helps to differentiate them from histologic mimics.

Acquired Digital Fibrokeratoma

Clinical Features

Acquired digital fibrokeratoma, also known as acral fibrokeratoma, is a benign entity most commonly located on fingers or toes, and less often on palms or soles. The clinical presentation is that of a solitary elongated or pedunculated

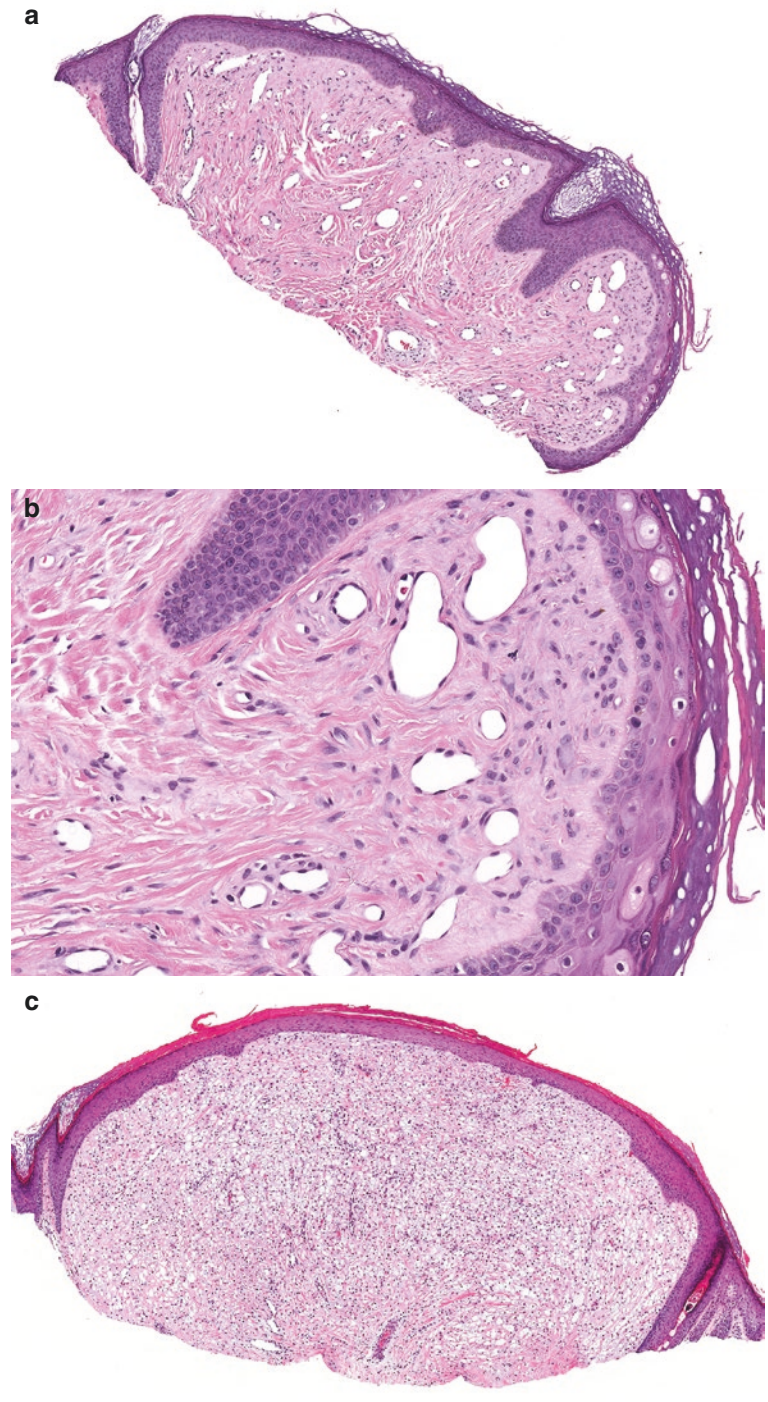
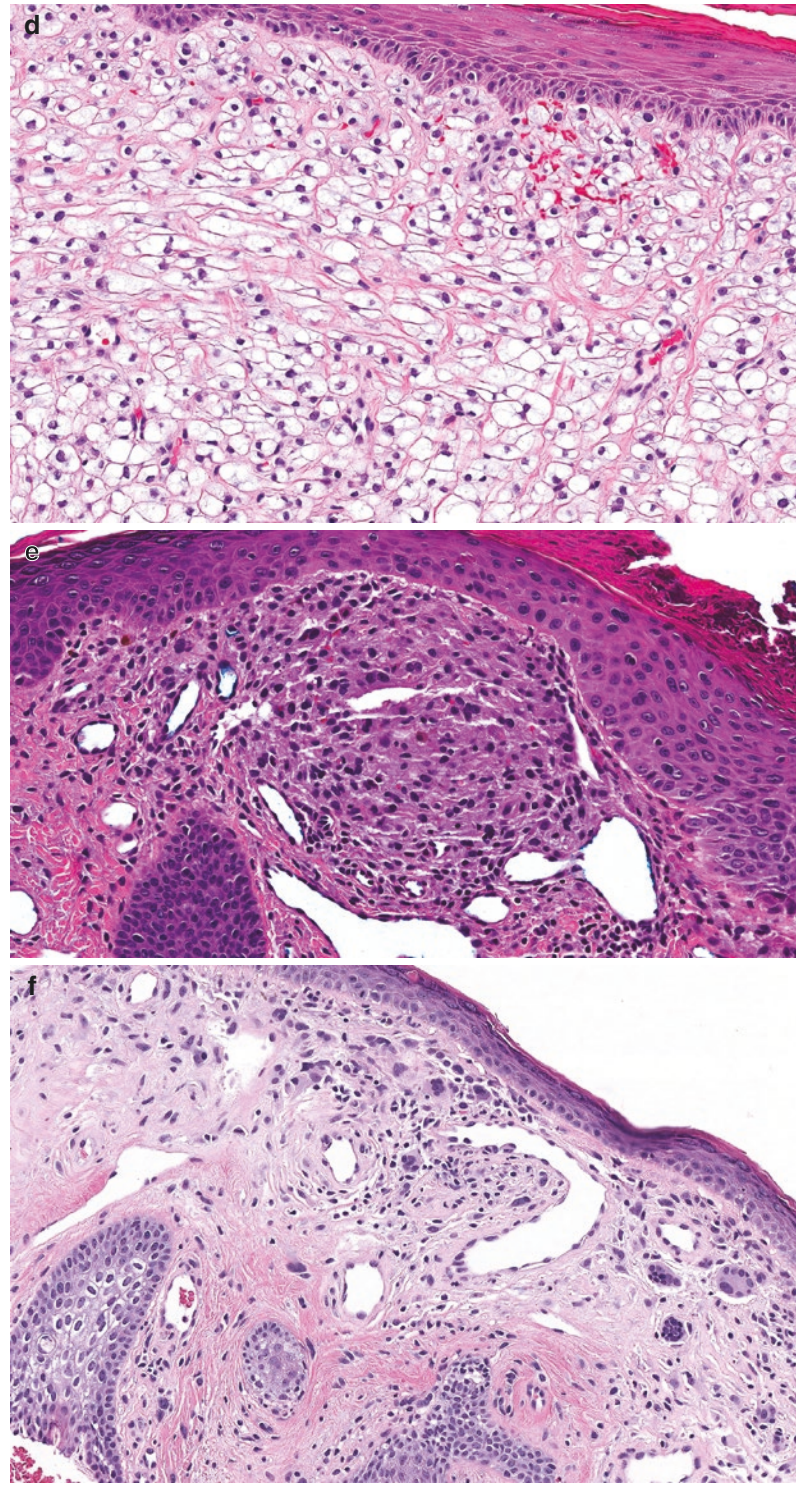


Fig. 4.2 Superficial angiofibroma. (**a**) Fibrous papule with a dome-shaped, paucicellular proliferation of stellate-shaped fibroblasts within a dense fibrous stroma. (**b**) Occasionally, multinucleated cells may be seen. (**c**, **d**) Clear cell fibrous papule containing a proliferation of round cells with foamy clear cytoplasm resembling foamy macrophages or epithelial cells with clear cell change. (**e**) Granular cell fibrous papule is similar to the clear cell variant but contains much coarser granules. (**f**) Pleomorphic fibrous papule contains stellate fibroblasts with bizarre pleomorphism. (**g**) Pigmented fibrous papule containing melanophages. This example is also pleomorphic. (**h**) Inflammatory fibrous papule has similar features to classic fibrous papule with the addition of a brisk inflammatory infiltrate. (**i**) Epithelioid fibrous papule contains epithelioid cells with abundant eosinophilic cytoplasm. (Images **e**–**i** courtesy of Dr. Doug Fullen, University of Michigan)

Fig. 4.2 (continued)



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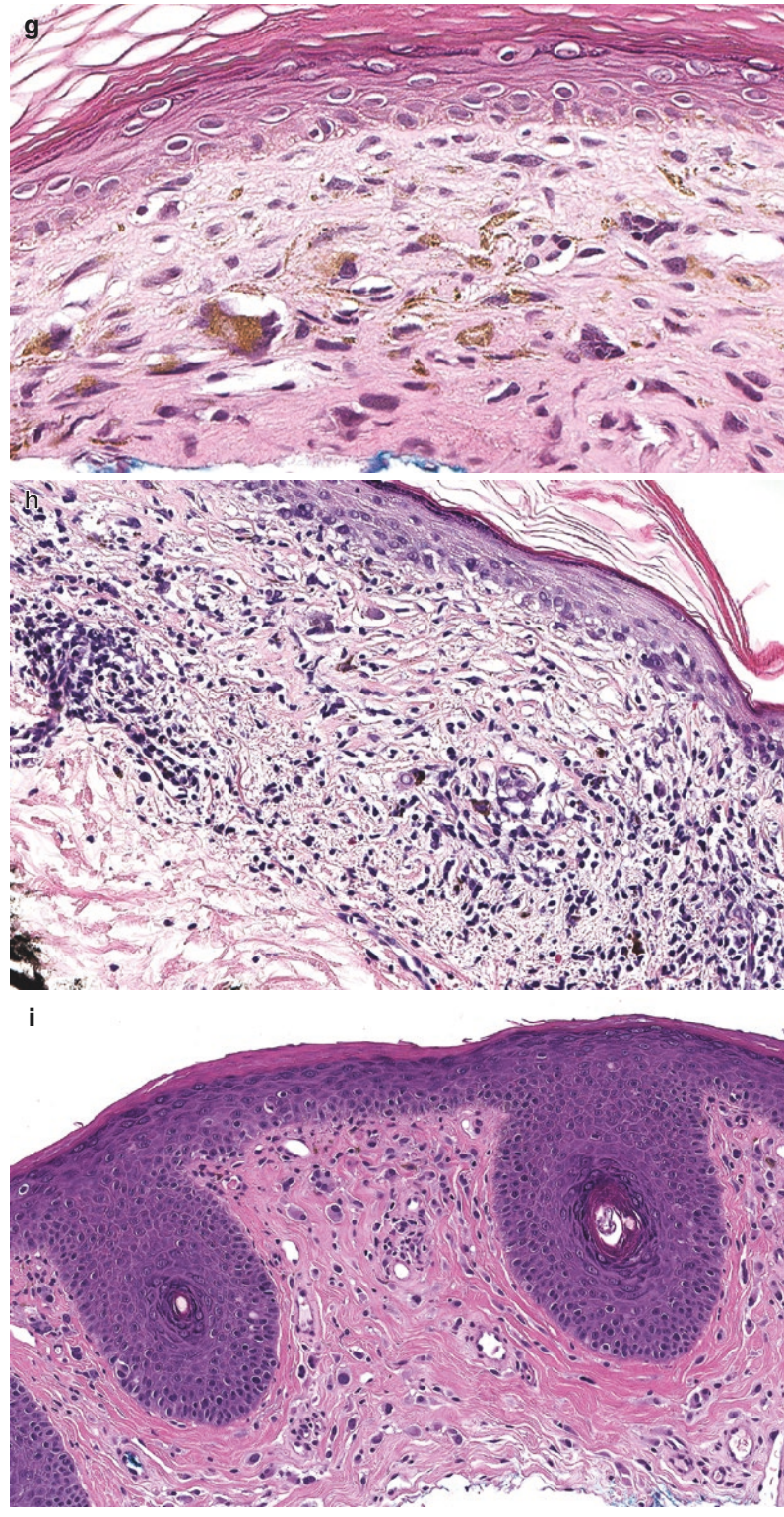


Table 4.2 Key histopathologic features: fibrous papule (angiofibroma)

Paucicellular proliferation of stellate-shaped fibroblasts within a dense fibrous stroma
Ectatic vessels
Occasionally multinucleated cells
Variants: hypercellular, clear cell, pigmented, pleomorphic, epithelioid, granular cell, and inflammatory
Stellate cells positive for FXIIIa, variable for CD68 and lysozyme, negative for S100 protein
CD34 positivity rare

growth with a collarette at the base. Dermoscopic evaluation can enhance visualization of the collarette and reveal a peripheral erythematous region with globular vessels, if this is not evident on initial clinical inspection. Generally, the lesions are small (5 mm or less), but they may become quite elongated, and giant variants have been described. A history of trauma is often present, but development during immunosuppressive therapy has also been noted. Treatment options include excision or laser ablation at the base of the lesion.

Pathologic Features

Histopathology reveals hyperkeratosis and acanthosis overlying thickened collagen bundles arranged along the vertical axis of the lesion. Interstitial fibroblasts are noted to course between collagen, and a characteristic pseudo-nail is often present (Fig. 4.3a and b). Different variants have been described, but all demonstrate the characteristic vertical orientation of collagen bundles. The origin of the lesion may be from dermal connective tissue or from the proximal nail fold and surrounding connective tissue, similar to periungual fibromas (Koenen tumor and "garlic clove" periungual fibroma) (Table 4.3).

Differential Diagnosis

The differential diagnosis includes cellular digital fibroma and superficial acral fibromyxoma, though both of these entities are more cellular and do not have a pseudo-nail. A supernumerary digit similarly appears on fingers or toes, classically on the fifth digit, but is identified by the presence of nerve bundles at its base.

Angiofibroma of Soft Tissue

Clinical Features

Angiofibroma of soft tissue is a distinct, recently described, benign soft tissue tumor with female predominance that typically occurs in middle-aged adults. Tumors usually present as a slowly enlarging painless superficial or deep soft tissue mass in the extremities. This lesion only rarely recurs after surgical excision.

Pathologic Features

Angiofibroma of soft tissue is circumscribed but unencapsulated. The tumors are variably cellular and predominantly comprised of bland-appearing spindle cells with scant pale to amphophilic cytoplasm, hyperchromatic tapered nuclei, and inconspicuous nucleoli. Tumor cells are arranged haphazardly within a variable fibromyxoid stroma with numerous admixed small thin-walled vessels (Fig. 4.4a and b). Scattered tumor cells may express EMA (50% of cases) and CD34, and SMA may be seen in a subset of cases. These tumors are typically negative for S100 protein, desmin, and pan-cytokeratin. Angiofibroma of soft tissue has a t(5;8)(q15;q13) resulting in an *AHRR-NCOA2* fusion (Table 4.4).

Differential Diagnosis

The differential diagnosis for angiofibroma of soft tissue is broad and includes benign, intermediate, and malignant soft tissue tumors, including myxoid dermatofibrosarcoma protuberans, solitary fibrous tumor, myxofibrosarcoma, myxoid liposarcoma, cellular angiofibroma, and low-grade fibromyxoid sarcoma. Myxoid dermatofibrosarcoma protuberans (DFSP) arises in the

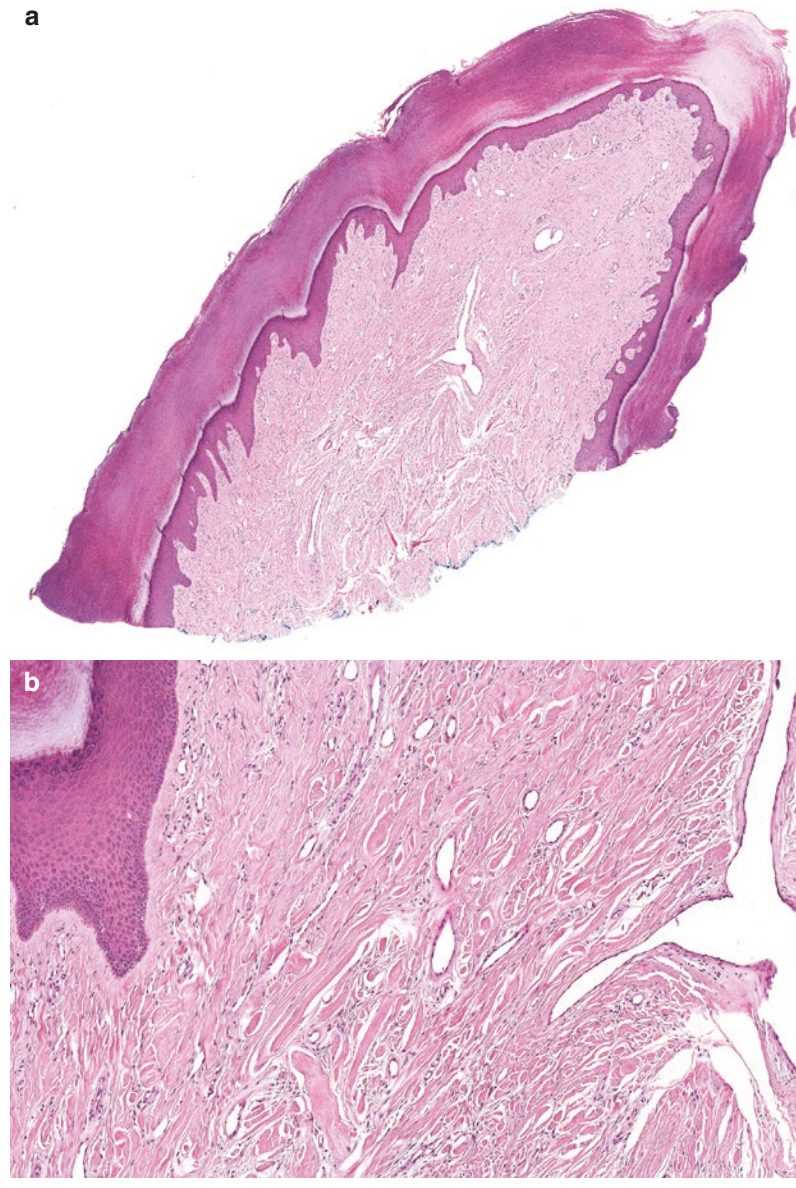


Fig. 4.3 Acquired digital fibrokeratoma. (**a**) Hyperkeratosis and acanthosis overlying vertically oriented collagen bundles. (**b**) Interstitial fibroblasts are present between collagen bundles

dermis, demonstrates fat infiltration, and often shows focal areas of conventional dermatofibrosarcoma protuberans. Solitary fibrous tumor has branching staghorn vessels and is immunoreactive for CD34 and STAT6. Myxofibrosarcoma is infiltrative and has more nuclear atypia and mitotic activity, and widely spaced curvilinear vessels, rather than abundant plexiform vessels. Myxoid liposarcoma has a delicate plexiform vasculature, less uniform cellularity, lipoblasts, and *DDIT3* rearrangement. Low-grade fibromyxoid sarcoma shows alternating fibrous and myxoid zones and is positive for MUC4. Cellular angiofibroma is more similar in name than clinicopathologic features. Unlike soft tissue

Table 4.3 Key pathologic features: acquired digital fibrokeratoma

Epidermal hyperkeratosis and acanthosis
Fibrovascular stroma
Thickened vertically oriented collagen bundles
Characteristic pseudo-nail is often present

angiofibroma, cellular angiofibroma arises most often in the genital region; contains thicker, more hyalinized blood vessels; and has abnormalities of 13q resulting in loss of RB1 expression by immunohistochemistry.

Pleomorphic Fibroma of the Skin

Clinical Features

First described by Kamino et al. in 1989, pleomorphic fibroma (PF) is a solitary, polypoid cutaneous lesion that most commonly arises in the extremities of adults. These lesions are asymptomatic, slow growing, and measure from a few millimeters up to 1.6 cm in greatest dimension. Patients are usually in their third to sixth decades of life, and there is a slight female predominance. Rare subungual cases have been described. These lesions behave in a benign fashion with only rare local recurrences reported. PF are cured by simple excision.

Pathologic Features

Histopathologically, lesions are small, dome-shaped or polypoid, centered in the dermis, densely fibrotic, and sparsely to moderately cellular (Fig. 4.5a). Constituent cells are stellate in shape and have large, pleomorphic, hyperchro-

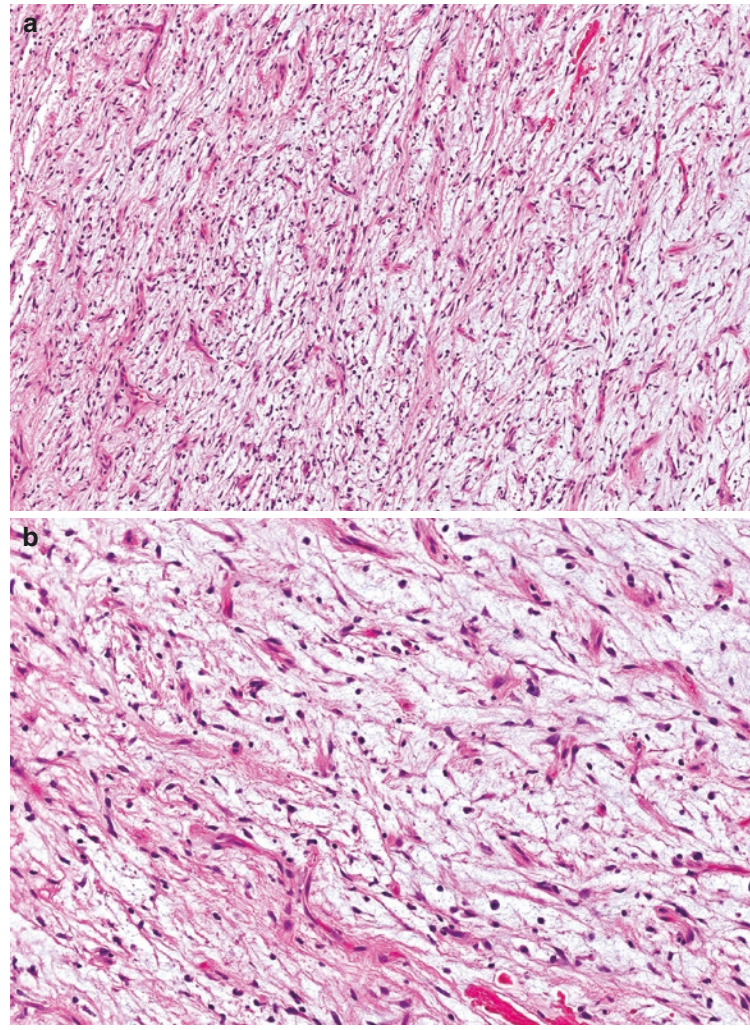


Fig. 4.4 Angiofibroma of soft tissue. (**a**) Bland-appearing spindle cells haphazardly arranged within a variable fibromyxoid stroma in association with small, thin-walled vessels. (**b**) A higher power view. (**c**) A transition zone between myxoid and more fibrous areas

Fig. 4.4 (continued)

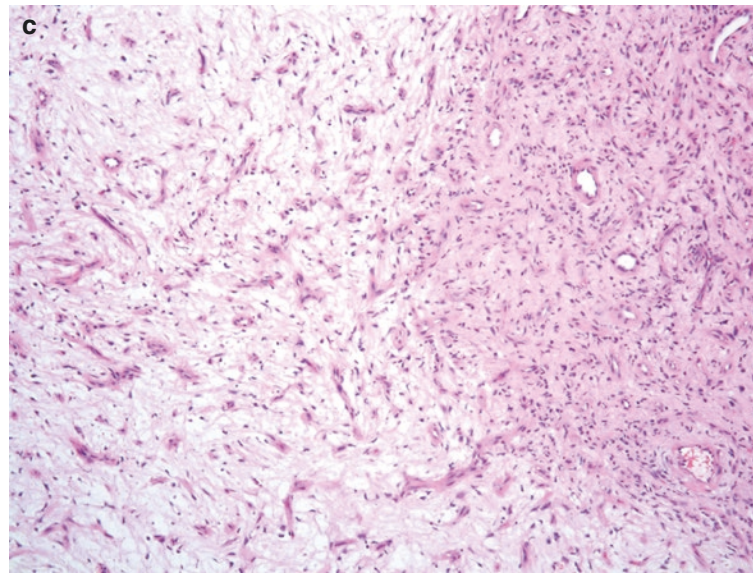


Table 4.4 Key pathologic features: soft tissue angiofibroma

Proliferation of bland, uniform spindle cells
Numerous branching thin-walled blood vessels
Variably myxoid to collagenous stroma
t(5;8) resulting in *AHRR-NCOA2* gene fusion

matic nuclei. Multinucleated cells may be seen (Fig. 4.5b and c). Mitotic figures, including atypical forms, are rarely encountered. A myxoid variant with abundant interstitial mucin has also been reported. The pleomorphic cells are positive for vimentin and CD34, while desmin and S100 protein are negative. Reported immunoreactivity for Factor XIIIa has been variable, with some cases showing positivity in pleomorphic cells, and others demonstrating negativity or only patchy positivity. A recent study demonstrated loss of *RB1* on chromosome 13q in pleomorphic fibromas and loss of RB1 protein expression by immunohistochemistry. These findings indicate that PF shares the same genetic abnormalities as spindle cell/pleomorphic lipoma and other mesenchymal tumors with 13q loss (Table 4.5).

Differential Diagnosis

Atypical fibrous histiocytoma is usually more cellular, has greater levels of nuclear atypia and pleomorphism, and demonstrates other typical features of a dermatofibroma, such as peripheral collagen trapping. Some pleomorphic fibromas have scattered adipocytes leading to consideration of an atypical lipomatous tumor in the differential. These lesions are very rare in the skin and usually spread into the dermis from a deeper-seated lesion. The adipocytic foci in PF lack evidence of cytologic atypia and likely represent entrapped fat cells. In addition, although rare cases of MDM2-positive PFs have been reported, FISH is negative for *MDM2* amplification. Also, atypical lipomatous tumor/well-differentiated liposarcoma does not demonstrate RB1 loss. Atypical fibroxanthoma and pleomorphic dermal sarcoma are usually much more cellular, show significantly more cytologic atypia, and have greater mitotic activity.

Gardner-Associated Fibroma

Clinical Features

Gardner-associated fibroma (GAF) is a benign fibrous soft tissue tumor that is associated with familial adenomatous polyposis (FAP) and desmoid-type fibromatosis. It has a predilection for children and adolescents. Approximately 78% of these lesions appear in the first decade of life (mean age, 5 years). There is a slight male predominance, and lesions are typically solitary,

arising in the back and paraspinal region. GAF serve as a sentinel lesion, helping to identify FAP patients who are at a high risk for developing desmoid fibromatoses.

Pathologic Features

GAF is a hypocellular proliferation composed of haphazardly arranged, thickened collagen fibers punctuated by occasional, bland fibroblastic spindle cells, small blood vessels, and mast cells (Fig. 4.6). Nerves, muscle, and adipose tissue are often entrapped at the periphery. The traumatic neuroma-like proliferation of nerve twigs of nuchal-type fibromas is not seen in GAF. By immunohistochemistry most lesions express CD34 and have nuclear immunoreactivity for beta-catenin (approximately 64% of cases in the largest study). The latter finding indicates dysregulation of the Wnt pathway either through *APC* or *CTNNB1* mutations (Table 4.6).

Differential Diagnosis

GAF are benign lesions, which may recur when incompletely excised. As noted previously, these lesions are associated with desmoid tumors but can be separated from them by the latter's increased cellularity arranged in long, intersecting fascicles. The main differential diagnosis is with nuchal-type fibroma. These typically arise in the cervical region of middle-aged adults,

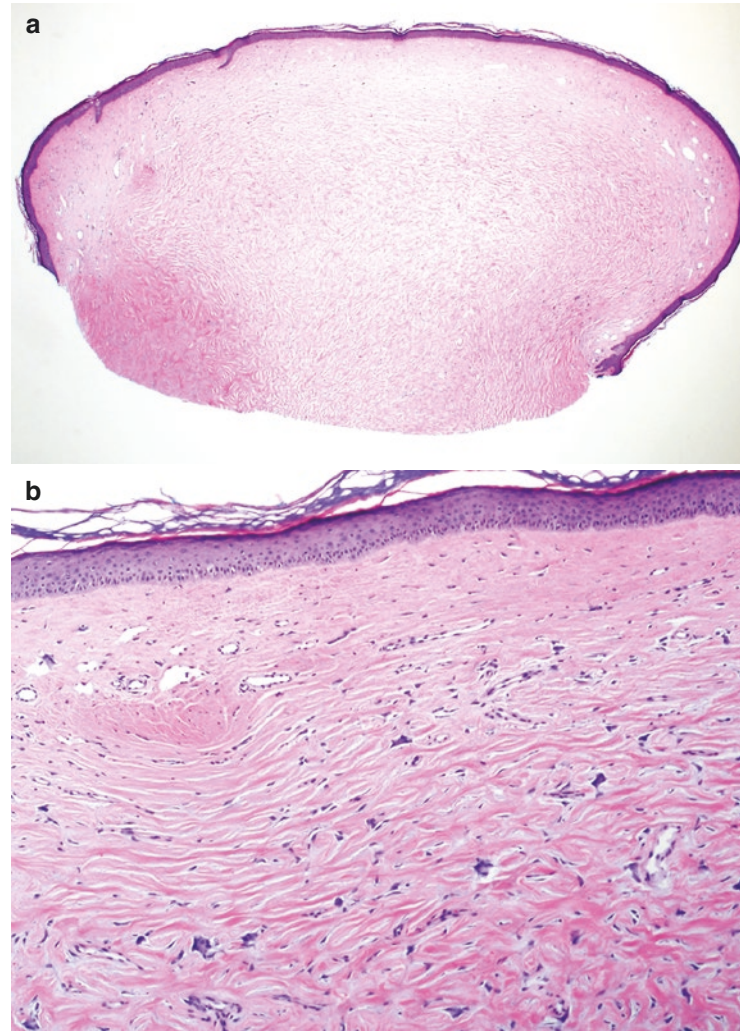
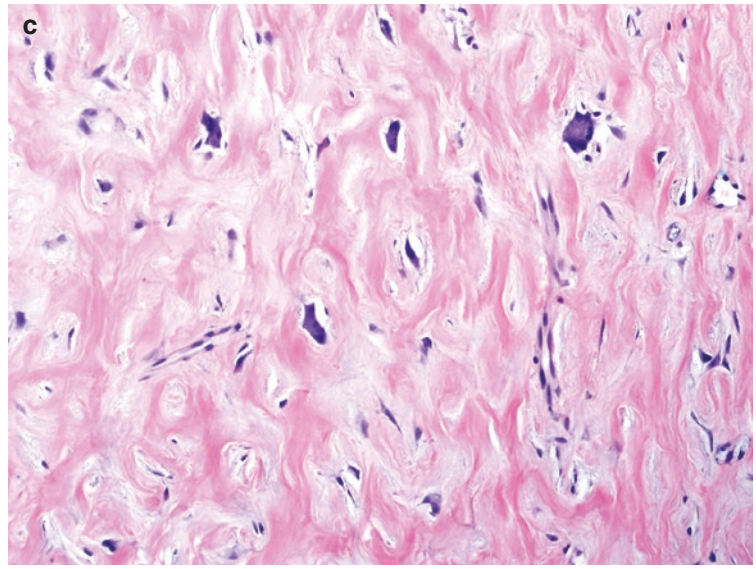


Fig. 4.5 Pleomorphic fibroma. (**a**) A polypoid lesions composed of a densely fibrotic stroma. (**b**, **c**) Constituent cells are stellate with large pleomorphic and hyperchromatic nuclei and are not uncommonly multinucleated. (Images courtesy of Dr. Karen Fritchie, Mayo Clinic)

Fig. 4.5 (continued)



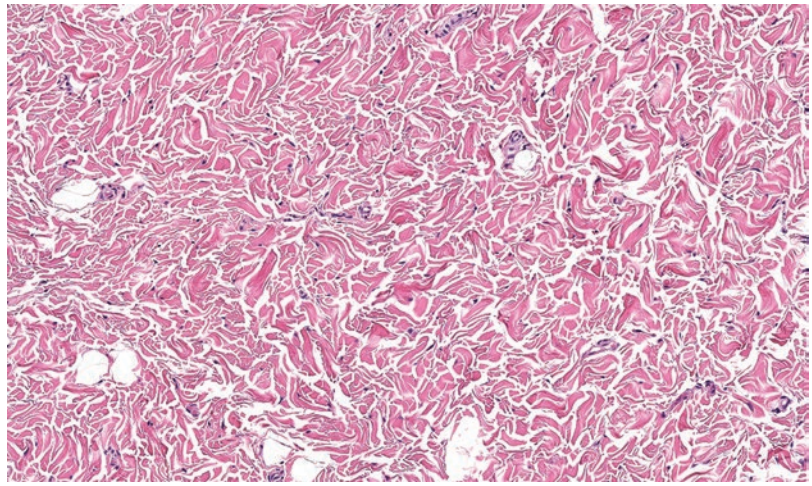


Fig. 4.6 Gardner-associated fibroma. A hypocellular proliferation of haphazardly arranged thickened collagen fibers punctuated by scattered bland fibroblastic spindle cells, occasional small blood vessels, and scattered mast cells

Table 4.5 Key pathologic features: pleomorphic fibroma of the skin

Small, well-circumscribed, dome-shaped, or polypoid lesion
Sparsely to moderately cellular with fibrotic collagen
Stellate cells with large hyperchromatic nuclei
Multinucleated cells may be seen
Pleomorphic cells positive for vimentin and CD34, FXIIIa variable
Desmin and S100 protein negative
Rb1 loss in pleomorphic cells

Table 4.6 Key pathologic features: Gardner-associated fibroma (GAF)

Associated with desmoid and FAP (Gardner syndrome)
Disorganized, thickened collagen bundles and scattered bland spindled fibroblastic cells
Adipose tissue, nerve tissue, and skeletal muscle may be entrapped at the periphery
No traumatic neuroma-like areas
Positive for CD34 and nuclear beta-catenin in 64% of cases

although other sites may also be involved (sacral region, extremities, buttocks). Nuchal-type fibromas are typically solitary lesions that are nearly histologically identical to GAF, but are more likely to have an increased number of entrapped nerve twigs.

Nuchal Fibroma

Clinical Features

Nuchal-type fibroma (NTF) is a rare fibrocollagenous lesion that arises in the posterior neck of middle-aged adults with a slight male predominance. NTF is strongly associated with diabetes mellitus (up to 44% of patients). Other sites of involvement have been reported, and up to 30% of cases include the chest, back, face, and extremities. Earlier cases of NTF were reported in association with Gardner syndrome. However, the clinicopathologic features of NTF are felt to be distinct from Gardner-associated fibroma (see above). NTF are benign lesions that may locally recur after incomplete excision.

Pathologic Features

NTF is typically a solitary, encapsulated, subcutaneous mass composed of a paucicellular proliferation of dense, haphazardly arranged bundles of collagen and scattered fibroblast cells, which entrap lobules of adipose tissue (Fig. 4.7a). Entrapment of adnexal structures and nerve bundles is seen, and there is often a traumatic neuroma-like proliferation of small nerve twigs at the periphery of the lesion (Fig. 4.7b). Constituent spindle cells are positive for CD34 and negative for actin and desmin. Beta-catenin is typically negative. A rare *APC* gene missense mutation and a very rare *MUTYH* gene polymorphism have been reported in one case of extra nuchal-type fibroma (Table 4.7).

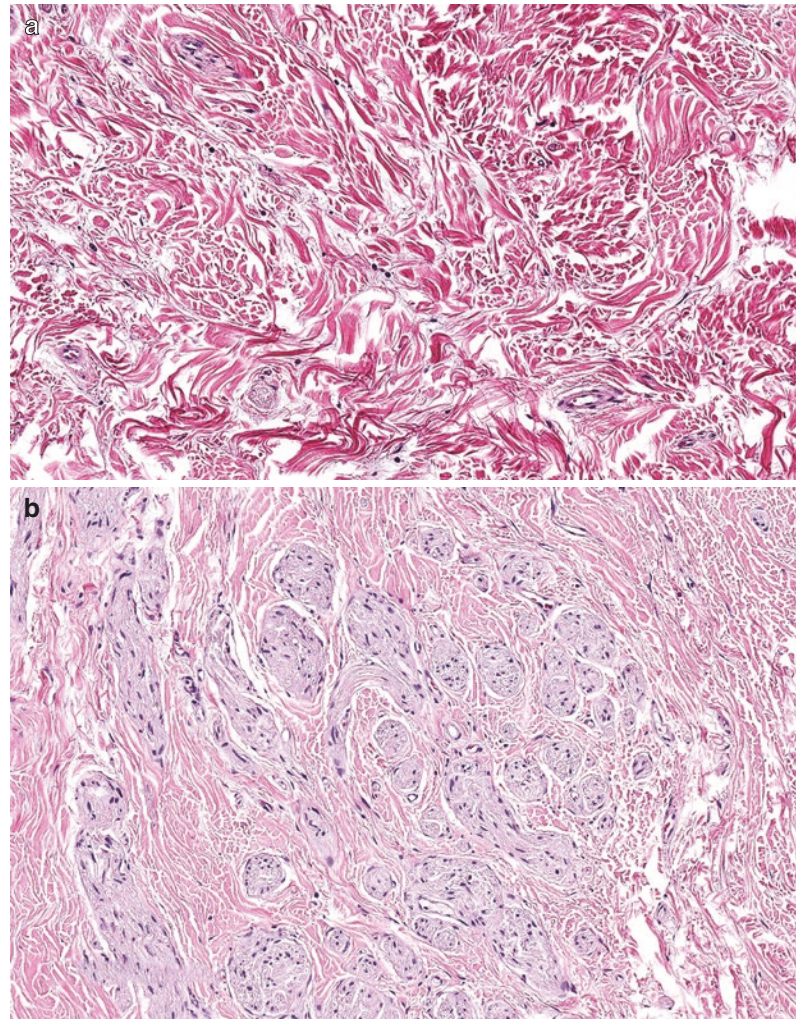


Fig. 4.7 Nuchal-type fibroma. (**a**) A paucicellular proliferation of dense, haphazardly arranged bundles of collagen admixed with scattered fibroblast-like cells and entrapped lobules of adipose tissue. Note the similarity to Gardner-associated fibroma. (**b**) Traumatic neuroma-like area in nuchal-type fibroma

Table 4.7 Key pathologic features: nuchal-type fibroma

Poorly circumscribed mass, 1–8 cm in maximum dimension
Hypocellular with dense hyalinized collagen and fibroblastic cells
Entrapped lobules of adipose tissue
Traumatic neuroma-like changes
Nuclear beta-catenin positivity rare
Negative for S100, SMA, desmin, and EMA

Differential Diagnosis

NTF may be confused with other fibrocollagenous proliferations that contain focal areas of adipose tissue. Gardner-associated fibroma is the most histopathologically similar lesion. Gardner-associated fibroma usually arises in much younger patients, shows a predilection for males, is less likely to present as multiple lesions, and is associated with FAP. Gardner-associated fibromas are more often associated with nuclear beta-catenin positivity. Fibromatoses are more cellular and are less likely to arise in the subcutis. Finally, elastofibroma is a deeper soft tissue lesion associated with abnormal, fragmented elastic fibers and typically presents in the scapular region.

Calcifying Aponeurotic Fibroma

Clinical Features

Calcifying aponeurotic fibroma is a benign, locally infiltrative fibroblastic soft tissue tumor with a slight male predominance, which typically occurs in children and rarely adults. Lesions usually present as a slowly enlarging, painless superficial soft tissue mass of the hands or feet, most commonly the palm or fingers. They may rarely be found along aponeuroses, tendons, and/or fascia at other sites, including the thigh, knee, arm, and elbow. Radiographic imaging may demonstrate intratumoral mineralization. Although calcifying aponeurotic fibroma has a good clinical course, local recurrence after incomplete surgical excision is common (50% of cases). Metastasis and fibrosarcomatous transformation have been reported in exceptionally rare cases. Calcifying aponeurotic fibroma-like lesions has been reported in a family with Albright's hereditary osteodystrophy.

Pathologic Features

The tumors are unencapsulated and poorly circumscribed, dermal masses that often extend into adjacent subcutaneous fat and skeletal muscle (Fig. 4.8a). Microscopically, tumors show variable cellularity and are comprised predominantly of bland-appearing fibroblastic spindle cells with scant eosinophilic cytoplasm, enlarged and slightly irregular hyperchromatic nuclei, and indistinct nucleoli. Tumor cells are arranged in a variety of patterns, including small whorls and short fascicles, within a collagenous stroma. The central portion of the tumor typically contains areas of calcification that are surrounded by epithelioid to chondroid tumor cells (Fig. 4.8b). Some cases may contain multinucleated cells and foci of bland cartilage. The spindle cells show variable SMA, muscle-specific actin, desmin, and CD68 staining, but are negative for S100 protein, beta-catenin, and CD34 expression; cartilaginous foci may express S100 protein. Rare cases may stain with CD34, progesterone receptor, CD57, and EMA. Calcifying aponeurotic fibroma has recurrent *FN1-EGF* fusions (Table 4.8).

Differential Diagnosis

The differential diagnosis for calcifying aponeurotic fibroma includes calcifying fibrous pseudotumor, fibro-osseous pseudotumor of digits, soft tissue chondroma, superficial fibromatosis, and infantile fibromatosis (lipofibromatosis). Although calcifying fibrous pseudotumor, fibro-osseous pseudotumor of digits, and calcifying aponeurotic tumor may have overlapping clinical and morphologic features, specific findings may be helpful for diagnosis (see below). In general, the presence of central cartilage formation with

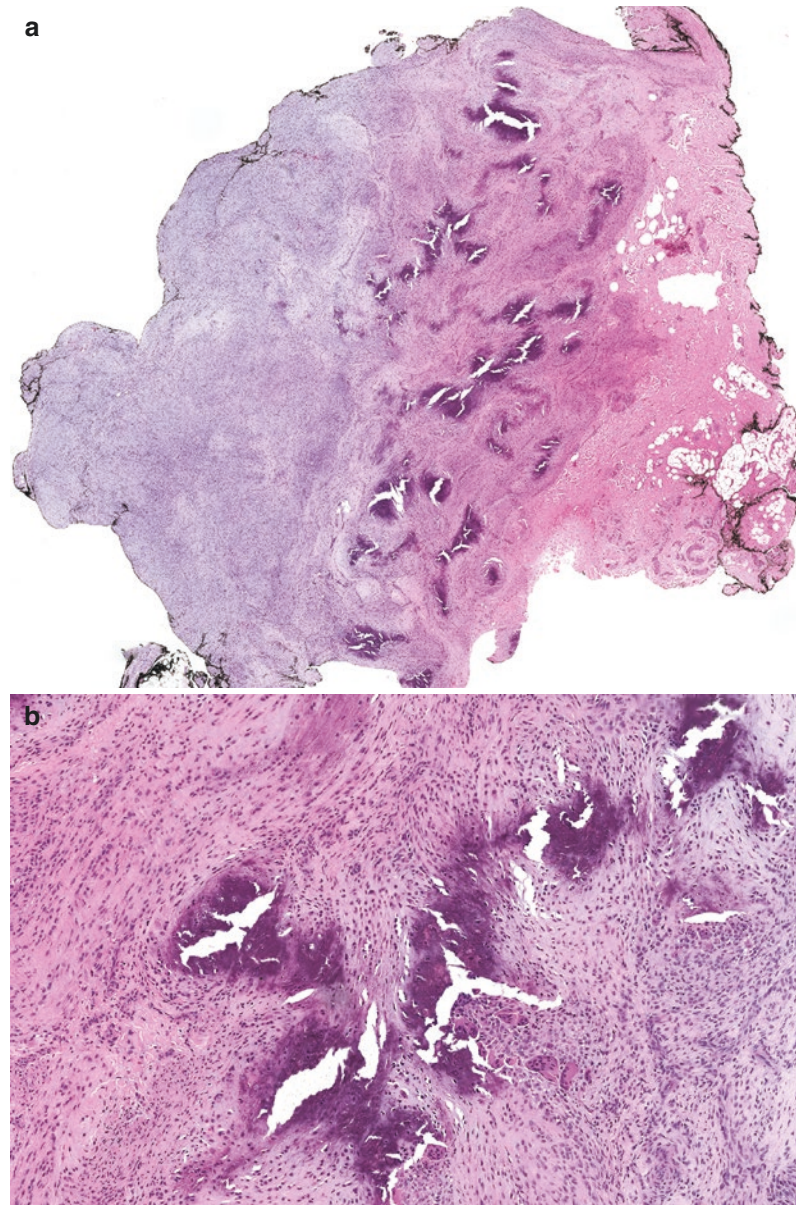


Fig. 4.8 Calcifying aponeurotic fibroma. (**a**) A poorly circumscribed, superficial soft tissue mass extending into adjacent subcutaneous fat and skeletal muscle. (**b**) Bland fibroblastic spindle cells present in whorls and fascicles in a collagenous stroma in association with a central calcified zone surrounded by a radial array of epithelioid to chondroid tumor cells

Table 4.8 Key pathologic features: calcifying aponeurotic fibroma

Spindled-to-ovoid cells arrayed in parallel fascicles
Epithelioid/chondroid cells surrounding calcified zones
Foci of cartilage and multinucleated cells may be seen in some cases
Spindle cells show variable SMA, muscle-specific actin, desmin, and CD68 positivity, negative for S100 protein, beta-catenin, and CD34
Recurrent *FN1-EGF* fusions

calcification favors a diagnosis of calcifying aponeurotic fibroma. Conversely, fibromatosis is more cellular, only rarely shows calcifications, and is not associated with a cartilaginous component. While soft tissue chondromas are benign cartilaginous soft tissue tumors that may show calcification, the presence of an associated spindle cell component favors calcifying aponeurotic fibroma. Unlike calcifying aponeurotic fibroma, infantile fibromatosis (lipofibromatosis) shows

fascicles of spindle-to-ovoid cells in a myxoid background infiltrating atrophic skeletal muscle and lipocytes. It has no cartilaginous areas and does not calcify.

Elastofibroma

Clinical Features

Elastofibroma is a benign soft tissue pseudotumor with a strong female predominance that typically presents in elderly adults. A familial predisposition for elastofibroma is seen in up to one third of cases. It usually presents as a slowly growing painless deep soft tissue mass in the upper back near the scapula and may frequently be present bilaterally. There is often a prior history of repetitive trauma, such as intense manual labor. Tumors do not recur after surgical excision.

Pathologic Features

Elastofibromas are unencapsulated, poorly circumscribed hypocellular lesions comprised of bland-appearing fibroblastic spindle cells within dense collagen that contain bundles of degenerated elastic fibers. The elastic fibers have a characteristic serrated and beaded appearance, which can be highlighted with an elastic stain (Fig. 4.9a and b). Admixed lobules of mature adipose tissue may impart a pseudoinfiltrative appearance. The spindle cells are variably positive for CD34 and negative for SMA, desmin, and S100 protein. A variety of chromosomal abnormalities have been reported in elastofibroma including alterations to chromosome 1, t(8;12)(q22;q24.3), copy gains of Xq and t(2;19), and (X;1) rearrangements (Table 4.9).

Differential Diagnosis

The diagnosis of elastofibroma is rarely problematic. Desmoplastic fibroblastoma is perhaps the closest mimic, but the stellate cells of this entity and the lack of altered elastic fibers allow distinction. An elastic stain will confirm the diagnosis of elastofibroma in problematic cases.

Desmoplastic Fibroblastoma (Collagenous Fibroma)

Clinical Features

Desmoplastic fibroblastoma (DFB)/collagenous fibroma is a slow-growing firm mobile mass that rarely causes pain and typically arises in the deep subcutaneous tissue, fascia, or skeletal muscle in adults. It was probably reported as a variant of a fibroma, or other benign mesenchymal tumor in the literature, before the seminal description by Harry Evans in 1995. Patients are usually in the fifth to seventh decades of life, with lesions only rarely being reported in children and adolescents. Males are affected at least twice as commonly as females. Common sites of involvement include the upper and lower extremities, and lesions rarely arise in the head and neck region.

Pathologic Features

Most DFB are well-circumscribed, paucicellular, and composed of distinct, stellate, and bipolar spindle cells, which are widely spaced within a myxocollagenous stroma and demonstrate little to no atypia or mitotic activity (Fig. 4.10a and b). Immunohistochemistry is rarely helpful in making the diagnosis, with at most focal immunoreactivity for SMA and muscle specific actin. Stains for CD34, desmin, and S100 protein are negative. Rare cytokeratin positive cells may be seen. Recently, it has been reported that DFB is positive for FOSL1, a member of the FOS family encoding leucine zipper proteins, by immunohistochemistry, distinguishing this lesion from fibroma of tendon sheath, a morphologic mimic. Genetic abnormalities involving 11q12 are reportedly common in DFB. Though abnormalities involving 11q have also been reported in fibroma of tendon sheath, it is uncertain whether this finding is indicative of a close link between the two lesions (Table 4.10).

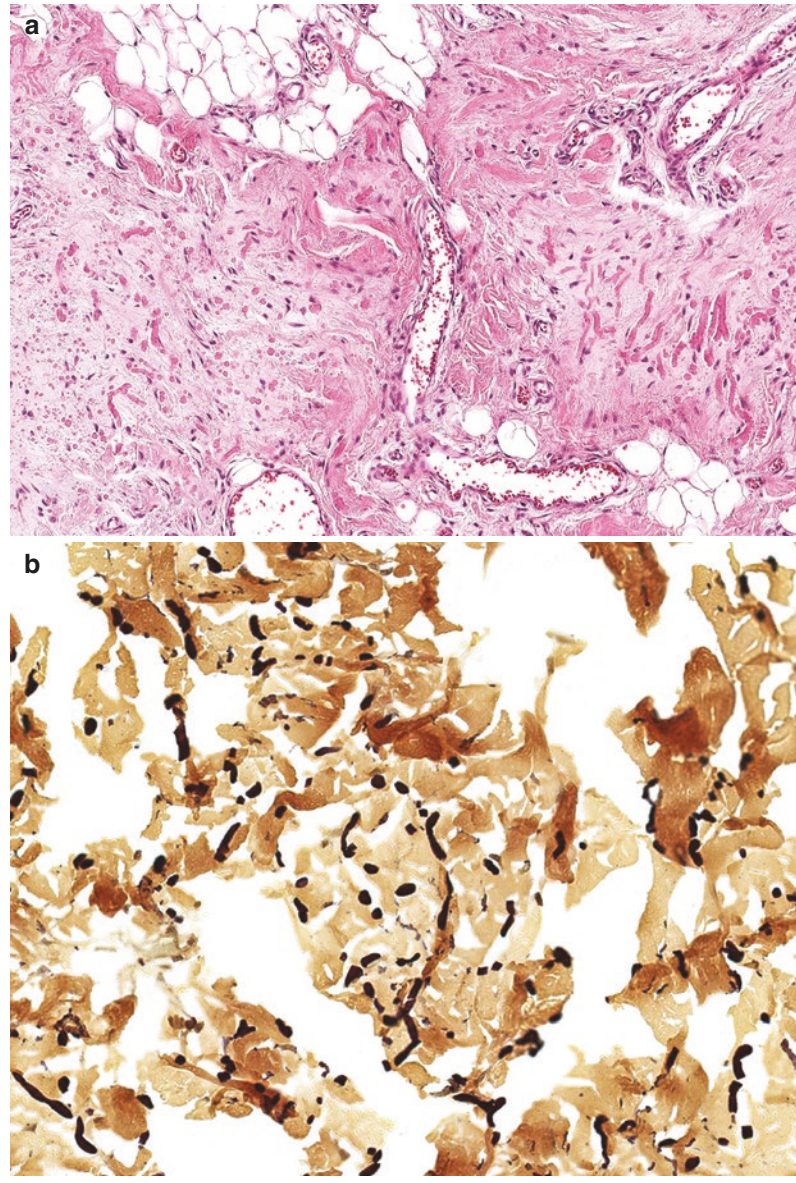


Fig. 4.9 Elastofibroma. (**a**) Bland-appearing fibroblastic spindle cells within dense collagen containing bundles of degenerated elastic fibers with a characteristic serrated and beaded appearance. (**b**) Elastic stain highlighting fibers in black

Table 4.9 Key pathologic features: elastofibroma

Fibroblasts, collagen, and degenerating elastic fibers
Elastic fibers with serrated or beaded appearance
Elastic fibers stain with elastic stain, fibroblasts variably CD34-positive

Differential Diagnosis

A variety of benign and low-grade malignant mesenchymal tumors are in the differential diagnoses. The differential of elastofibroma is discussed above. Fibromatoses are more cellular and have a distinct fascicular growth pattern, infiltrate surrounding tissues, and may have scattered perivascular lymphocytes. Low-grade fibromyxoid sarcoma is more cellular, demonstrates distinct abrupt transition between hypercellular myxoid areas and more hypocellular fibrotic areas, and is positive for MUC4. Calcifying fibrous pseudotumor affects young adults and children and typically contains psam-

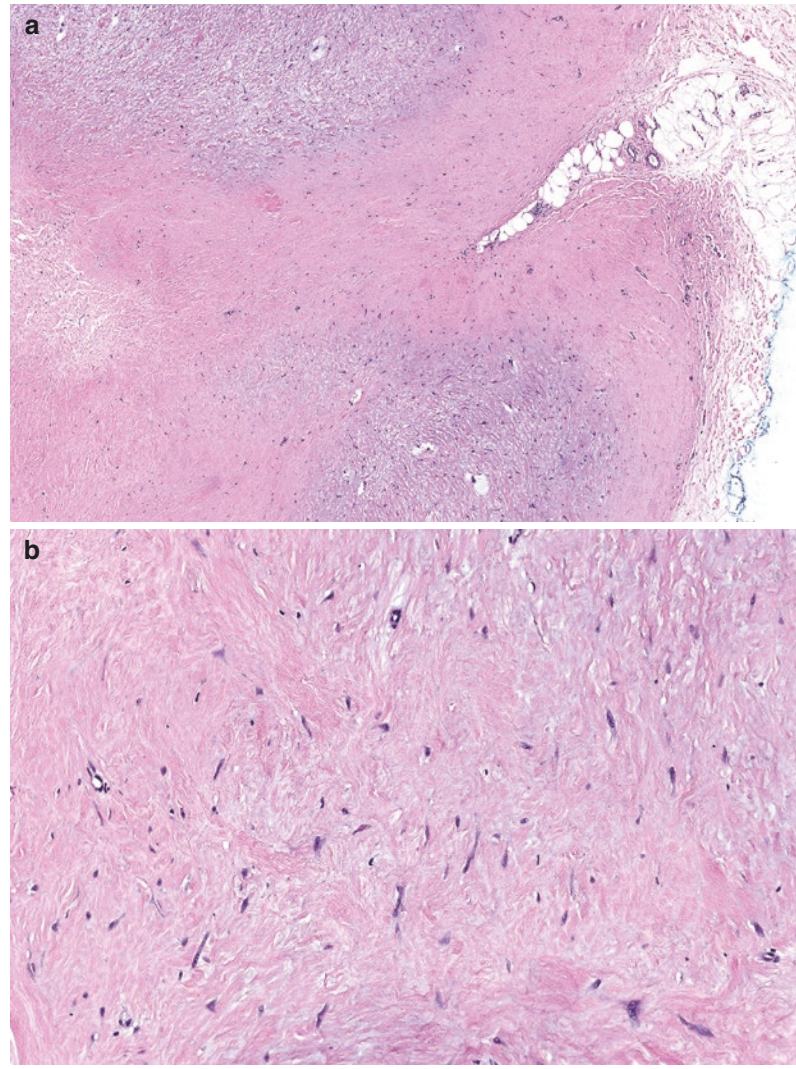


Fig. 4.10 Desmoplastic fibroblastoma (collagenous fibroma). (**a**) Well-circumscribed, paucicellular lesion composed of distinct, widely spaced, stellate to bipolar spindle cells. (**b**) Higher-power view of stellate cells in a dense myxocollagenous to collagenous stroma

Table 4.10 Key pathologic features: desmoplastic fibroblastoma (collagenous fibroma)

Abundant hypovascular myxocollagenous or collagenous stroma
Low to moderately cellular proliferation of uniformly distributed bipolar-to-stellate cells with small nucleoli
No significant atypia; mitoses uncommon
Positive for FOSL1 and focally positive for SMA and muscle specific actin; negative for S100, CD34, desmin, and EMA. Rare keratin-positive cells may sometimes be seen
t(2;11)(q31;q12) reportedly common

momatous calcifications and a lymphoplasmacytic infiltrate. Hypocellular or myxoid variants of neurofibroma may resemble DFB, but there is usually a characteristic combination of fine collagen fibers with bland spindle cells with wavy buckled nuclei and scattered mast cells. Neurofibromas are also strongly and diffuse positive for S100 protein unlike DFB. Older lesions of nodular fasciitis may become hyalinized and somewhat more paucicellular. However, typical cellular areas of nodular fasciitis with a tissue

culture-like growth pattern, myxoid degeneration, and extravasated erythrocytes are usually present to allow distinction.

Sclerotic Fibroma (Storiform Collagenoma)

Clinical Features

Sclerotic fibroma (SF) is a distinctive benign cutaneous fibrous lesion that typically presents as a slow-growing, firm, skin-colored to hyperpigmented solitary nodule. It may arise in any part of the body, but the head and neck region and arms are commonly affected. Adults are typically affected with no gender preference. Multiple lesions are a marker of Cowden syndrome (a member of PTEN hamartoma tumor syndrome, which also includes Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome, and Proteus-like syndrome). These lesions may also be sporadic. Simple excision is curative.

Pathologic Features

SF is a well-demarcated, hypocellular dermal nodule made up of sclerotic collagen with extensive clefting artifact and containing a storiform proliferation of bland spindle cells (Fig. 4.11a). The storiform pattern is so extensive as to impart a "plywood-like" pattern, which has led some to describe these as plywood fibromas (Fig. 4.11b). Cases with bizarre multinucleated giant cells, myxoid change, and high cellularity have also been described. By immunohistochemistry the spindle cells express Factor XIIIa and SMA, and to a lesser extent CD34 (Table 4.11).

Differential Diagnosis

The differential diagnoses include sclerotic neurofibroma and dermatofibroma and hypocellular fibroma of tendon sheath. Unlike SF, neurofibroma is composed of S100 protein-positive spindle cells with wavy, buckled nuclei in association with collagen bundles and mast cells. Dermatofibroma may be distinguished from SF by the presence of features typical of the former including secondary elements (e.g., hemosiderin and foam-laden cells, Touton-type giant cells, etc.), peripheral collagen trapping, and epidermal hyperplasia. Fibroma of tendon sheath has clefting artifact similar to SF, but the former does not arise in the dermis, is usually intimately associated with tendon sheaths, has characteristic slit-like vessels, and resembles burnt-out nodular fasciitis at least focally.

Fibrous Hamartoma of Infancy

Clinical Features

Fibrous hamartoma of infancy (FHI) is a rare soft tissue lesion, which typically affects infants and young children. Classically, lesions involve the axilla, back, or upper arm, but unusual locations including the scrotum, chest wall, thigh, breast, forearm, abdominal wall, buttock, cheek, scalp, hip, and orbit have been reported. There is a strong male predominance, and the mean patient age is 15 months. Approximately 20% of cases may arise congenitally. These lesions are benign, with only local recurrences (15% of cases) reported and no metastases.

Pathologic Features

Histopathologically, these lesions display a classic triphasic morphology: fibrous bands composed of bland spindle-shaped fibroblasts and myofibroblasts in fascicles separated by collagen; more cellular, immature, round to spindled cells in a myxoid matrix; and variable amounts of mature adipose tissue (Fig. 4.12a–d). A recent large study from the Mayo Clinic reported cases with a resemblance to giant cell fibroblastoma and two tumors with sarcomatous features. The one sarcomatous case with follow-up showed the patient to be alive and well after radical resection 4 years after presentation. Fibroblastic cells are SMA-positive, but mesenchymal cells are nega-

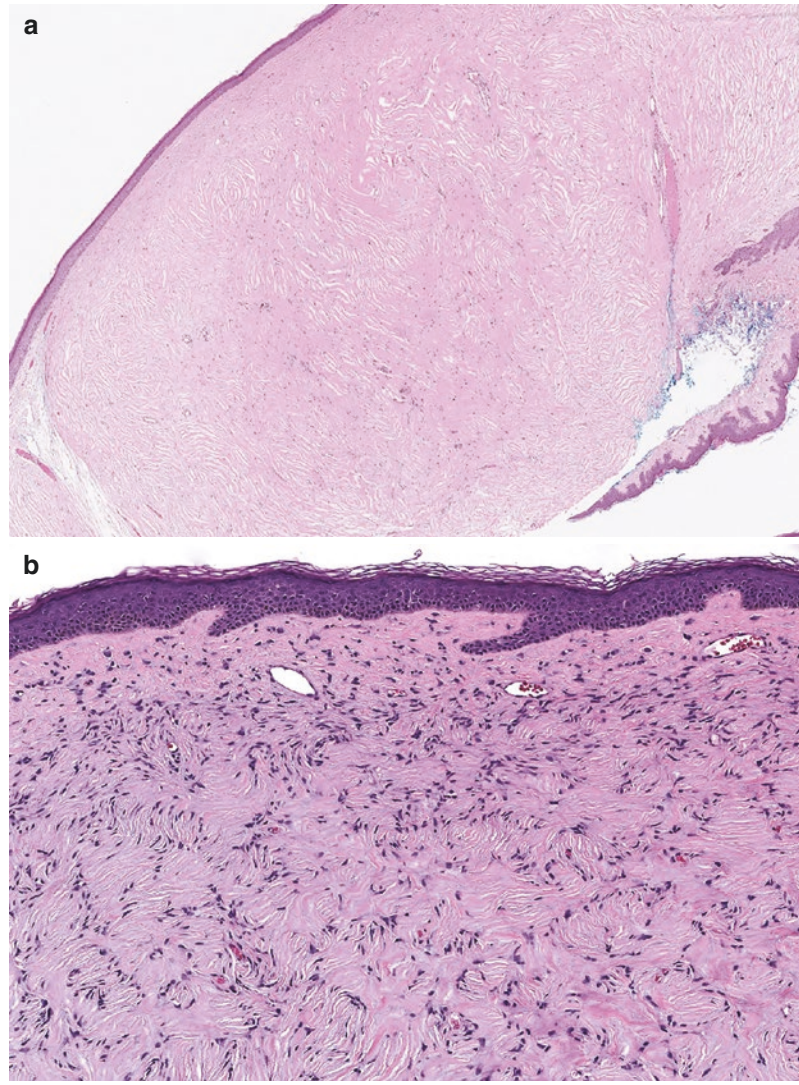


Fig. 4.11 Sclerotic fibroma (storiform collagenoma). (**a**) A well-demarcated hypocellular dermal nodule made up of a storiform proliferation of bland spindle cells embedded in sclerotic collagen with extensive clefting artifact. (**b**) The pattern of the stroma imparts a "plywood-like" pattern

Table 4.11 Key pathologic features: sclerotic fibroma

Polypoid, well-circumscribed lesion with abundant collagen
"Plywood-like" clefting artifact
Bland spindle cells in prominent storiform growth pattern
Myxoid change, multinucleated giant cells, and high cellularity may be seen
FXIIIa, SMA, and CD34 (variable)-positive; desmin, cytokeratin, and S100 protein are negative
Lesions associated with Cowden syndrome have loss of *PTEN* (10q23.3)

tive. The fibroadipose tissue is positive for S100, and sclerotic zones are CD34-positive. Little is known about the genetic events which cause this lesion. Small numbers of cases have been reported to show cytogenetic abnormalities, including complex karyotypes involving gains and losses of multiple chromosomes, a complex t(6; 12;8) (q25;q24.3;q13) and a reciprocal t(2;3) (q31;q21). The latter findings suggest that these lesions are neoplasms rather than hamartomas (Table 4.12).

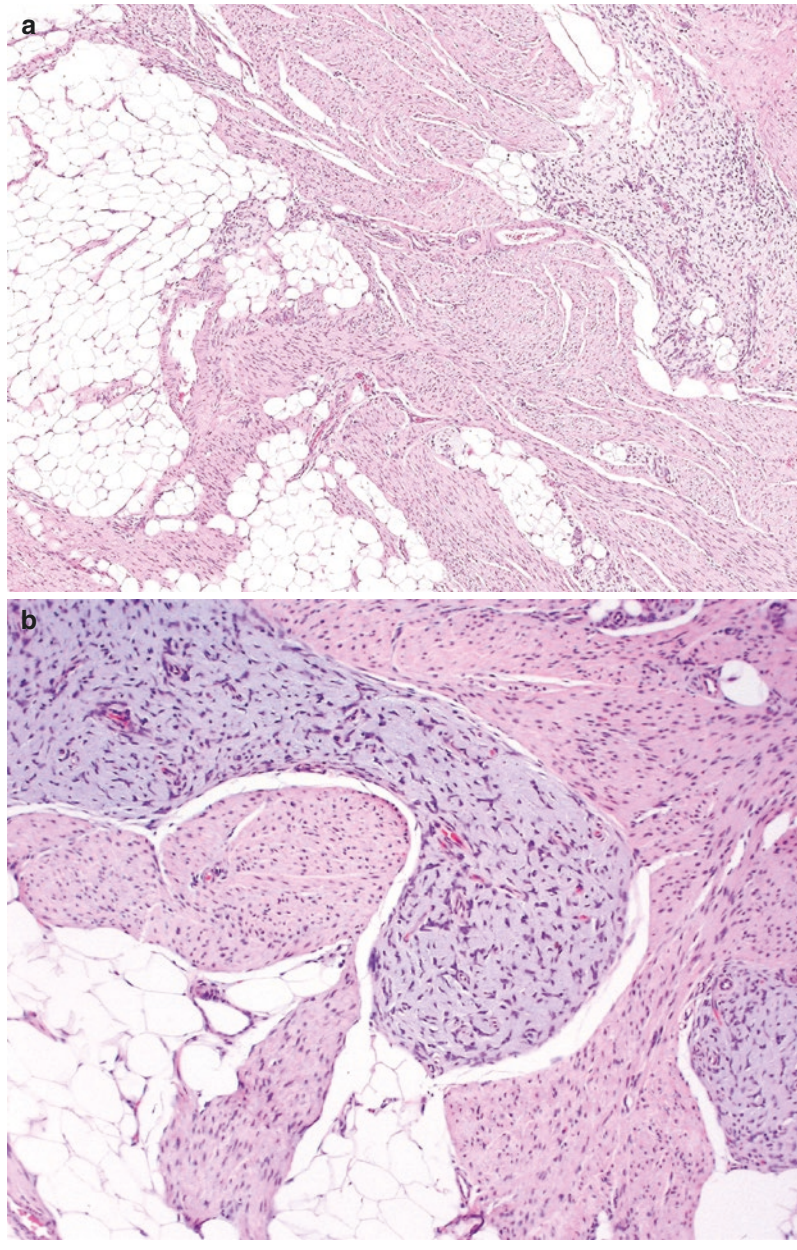


Fig. 4.12 Fibrous hamartoma of infancy. (**a**) Triphasic morphology consisting of fibrous bands composed of bland spindle cells, primitive spindled-to-ovoid mesenchymal cells, and variable amounts of mature adipose tissue. (**b**) High-power view of the three components of fibrous hamartoma: fibrous bands containing bland spindle cells, primitive mesenchymal cells, and adipose tissue. (**c**) High-power view of spindled-to-ovoid primitive mesenchymal cells. (**d**) An example of fibrous hamartoma with more adipose tissue

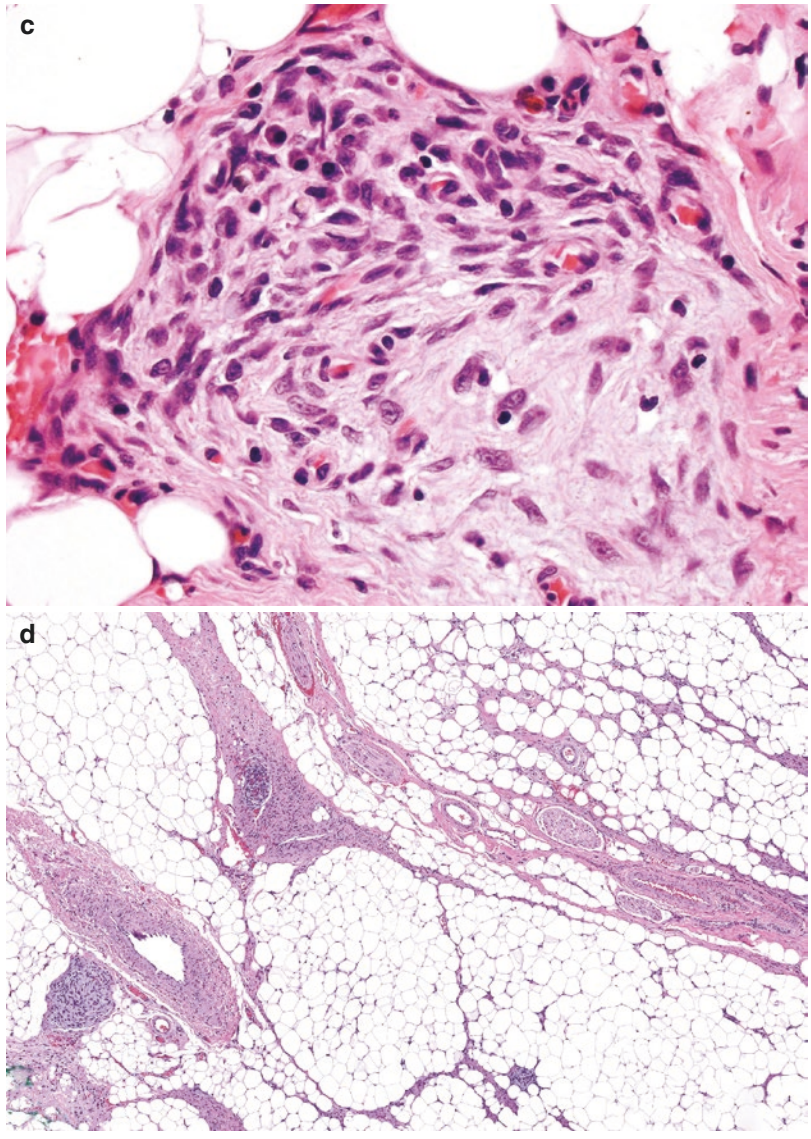


Fig. 4.12 (continued)

Table 4.12 Key histopathologic features: fibrous hamartoma of infancy

Classic triphasic morphology:
Bland fibroblastic myofibroblastic cells in fascicles
Myxoid nodules with primitive spindled to stellate cells
Varying amounts of adipose tissue

Differential Diagnosis

The differential is broad and includes tumors with varying amounts of adipose tissue, fibrous tissue, and primitive-appearing spindle cells. These lesions include lipofibromatosis, so-called lipofibromatosis-like neural tumor and maturing

lipoblastoma. Lipofibromatosis occurs on the distal extremities. "Lipofibromatosis-like neural tumor" has S100 protein-positive spindle cells and *NTRK1* rearrangement. Lipoblastoma tends to be circumscribed and has *PLAG1* rearrangements. The predominantly fibroblastic lesions in the differential include fibromatosis, myofibroma, and calcifying aponeurotic fibroma. Fibromatosis lacks the triphasic appearance, and many cases have nuclear beta-catenin localization. Myofibroma has a biphasic appearance with dark- and light-staining areas. Calcifying aponeurotic fibroma has zones of calcification surrounded by epithelioid to chondroid cells. Those rare cases with sarcomatous areas need to be distinguished from infantile fibrosarcoma and spindle cell rhabdomyosarcoma by documenting the absence of *ETV6* rearrangement and myogenin or MyoD1 expression, respectively.

Infantile Digital Fibroma (Inclusion Body Fibromatosis)

Clinical Features

Infantile digital fibroma/fibromatosis (IDF) is a benign myofibroblastic proliferation described in 1965 by Reye, also known as Reye's tumor or inclusion body fibromatosis. IDF occurs as small (<2 cm), dome-shaped, non-tender, single, or multiple nodules on the fingers and, less commonly, toes. The lesion favors the dorsal or lateral aspect of the distal digit, with the second to fifth digits most commonly affected. Involvement of the thumb or great toe is exceptional. Nearly all lesions present before the age of 3 years with most presenting within the first year of life.

Although there is a high rate of recurrence following surgery (up to 74%), IDF carries an excellent prognosis. Interestingly, many lesions will spontaneously regress given adequate time. Therefore, in the absence of rapid growth or functional impairment, some authors suggest expectant management. Additionally, intralesional corticosteroids may be helpful in the treatment of IDF.

Pathologic Features

On histopathology, IDF is a poorly circumscribed, uniform proliferation of bland fibroblasts within a dense collagenous stroma. This dermal-based proliferation surrounds adnexal structures and extends into the deep dermis and subcutis (Fig. 4.13a and b). On closer inspection, characteristic small round eosinophilic inclusions of variable size (3–15 microns) are present within the cytoplasm of fibroblasts, separated from the nucleus by a thin clear zone (Fig. 4.13c).

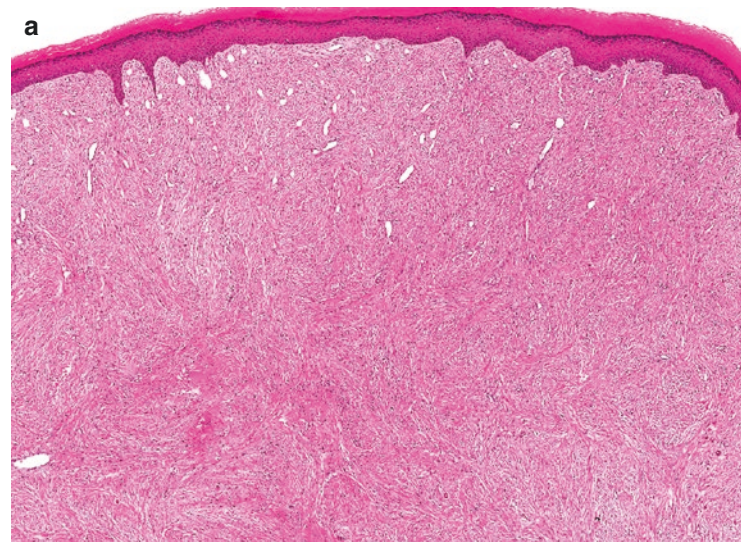


Fig. 4.13 Infantile digital fibroma (inclusion body fibromatosis). (**a**, **b**) A poorly circumscribed, uniform proliferation of bland fibroblasts within a dense collagenous stroma. (**c**) Characteristic small round eosinophilic inclusions of variable size (3–15 microns) are present within the cytoplasm of fibroblasts, separated from the nucleus by a thin clear zone. (**d**) Inclusions are highlighted on a trichrome special stain

Fig. 4.13 (continued)

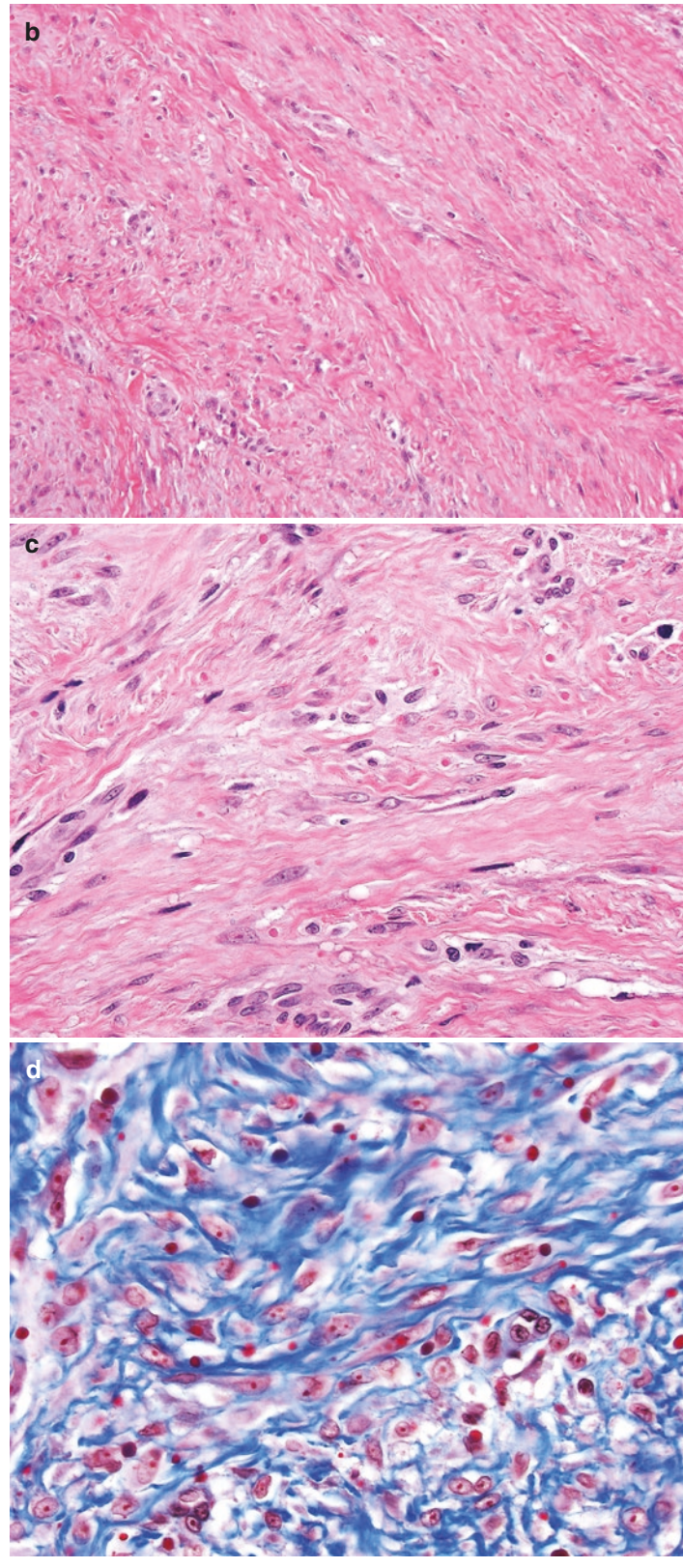


Table 4.13 Key pathologic features: infantile digital fibroma

Poorly circumscribed, uniform proliferation of bland fibroblastic cells in dense collagenous stroma
Lesional cells have round eosinophilic intracytoplasmic inclusions (3–15 microns)

Inclusions may be numerous or rare, in which case trichrome staining may be helpful in highlighting them (Fig. 4.13d). On ultrastructural and immunohistochemical examination, these inclusions have been shown to be densely packed actin microfilaments (Table 4.13).

Differential Diagnosis

The differential diagnosis includes palmoplantar fibromatosis, which lacks the characteristic eosinophilic inclusions. Benign digital fibromas (superficial acral fibromyxoma or cellular digital fibroma) may also be considered, but these lesions are typically seen in older patients and demonstrate diffuse CD34 immunoreactivity.

Plaque-Like CD34-Positive Dermal Fibroma

Clinical Features

Plaque-like CD34-positive dermal fibroma is a benign dermal spindle cell neoplasm first described by Rodriguez-Jurado and colleagues in 2004 as "medallion-like dermal dendrocyte hamartoma." Lesions are acquired or congenital, well-demarcated, slightly pigmented, indurated annular plaques that can affect any age group and arise at any anatomic site, with a slight female predominance. Clinical diagnoses typically included dermatofibroma, atrophic and plaque-like DFSP, and cutis laxa. There has been controversy regarding whether this is a neoplastic or hamartomatous lesion, or neither. However, recent work suggests that this is a neoplastic fibroblastic proliferation. This lesion is completely benign and cured by simple excision. Recurrence and malignant transformation have not been reported.

Pathologic Features

Lesions are composed of a band-like proliferation of bland, spindled fibroblasts in the mid to upper dermis. A grenz zone may be present, and extension into the subcutis is rare (Fig. 4.14a). Spindle cells in the superficial dermis are arrayed perpendicular to the epidermis, while deeper constituent cells take on a more storiform growth pattern. In areas, spindle cells are concentrically arrayed around the numerous capillaries. There is a paucity of elastic fibers, which may occasionally be entirely absent. Atypia is not appreciated, and mitoses are inconspicuous. A hypocellular variant of plaque-like CD34-positive dermal fibroma has been described. By immunohistochemistry the spindle cells are strongly and diffusely positive for CD34 and fascin (Fig. 4.14b). Immunoreactivity for SMA and FXIIIa is inconsistent at best (Table 4.14).

Differential Diagnosis

The differential diagnoses of plaque-like CD34-positive dermal fibroma include plaque-like and atrophic dermatofibrosarcoma protuberans, fibroblastic connective tissue nevus, diffuse neurofibroma, and dermatomyofibroma. Plaque-like and atrophic variants of dermatofibrosarcoma protuberans demonstrate clinical features similar to plaque-like CD34-positive dermal fibroma. The former entities are usually less well circumscribed both clinically and histopathologically, while the latter has a distinctly band-like, well-delineated proliferation within the papillary and upper reticular dermis. The perpendicular arrangement of superficial tumor cells alternating with parallel arrangement of deeper tumor cells of CD34-positive dermal fibroma is not seen in dermatofibrosarcoma protuberans. In difficult cases molecular studies for the *COL1A1-PDGFB* gene fusion allow for distinction between dermatofibrosarcoma protuberans and plaque-like CD34-positive dermal fibroma.

Fibroblastic connective tissue nevus also has a plaque-like clinical appearance and presents on the trunk of young adults and children but is composed

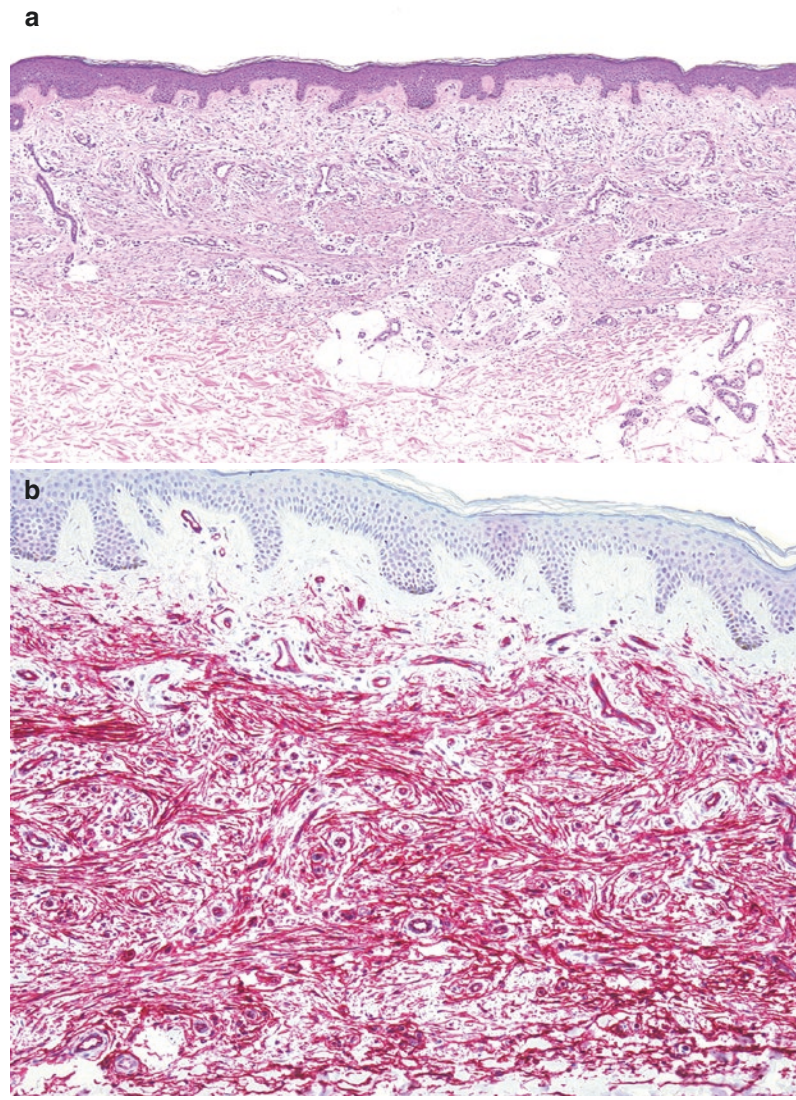


Fig. 4.14 Plaque-like CD34+ dermal fibroma. (**a**) A band-like proliferation of bland spindled fibroblastic cells in the mid to upper dermis beneath a grenz zone. Spindle cells in the superficial dermis are arrayed perpendicular to the epidermis (shown here), while deeper constituent cells take on a more storiform growth pattern. (**b**) CD34 immunostain is diffusely positive in the spindle cells. (Images courtesy of Dr. Thomas Mentzel, Dermatopathology Bodensee, Friedrichshafen, Germany)

Table 4.14 Key pathologic features: plaque-like CD34-positive dermal fibroma

Well-circumscribed spindle cell proliferation in papillary and reticular dermis with grenz zone
Cells oriented perpendicularly in superficial portions and parallel in deeper portion with respect to the epidermis
Diminished or absent elastic fibers
Scattered capillary vessels throughout
Rare mitotic figures and no atypia

of short fascicles of spindle cells present in a haphazard pattern involving the full thickness of the reticular dermis. Adnexal structures, vessels, and nerves may be entrapped, and there is often mature adipose tissue in the reticular dermis. The epidermis overlying the lesion is typically hyperplastic, unlike the epidermis in plaque-like CD34-positive dermal fibroma. Diffuse neurofibromas typically have more haphazardly arranged spindle cells in association with dermal collagen bundles and mast cells. Constituent cells have wavy and buckled, dark nuclei. Neurofibromas are positive for S100 protein. Unlike plaque-like CD34-positive dermal fibroma, dermatomyofibroma contains horizontally arranged, densely packed bundles and fascicles of bland spindle cells and is CD34-negative.

Dermatomyofibroma

Clinical Features

Dermatomyofibroma is an uncommon benign soft tissue tumor with a slight female predominance that typically occurs in young to middle-aged adults. Tumors usually present as slowly growing, painless cutaneous nodules or plaques involving the head and neck, thorax, or abdomen. These tumors only very rarely recur after surgical excision, even when incompletely excised. Rarely dermatomyofibroma may arise in children and be quite large or multicentric.

Pathologic Features

Microscopically, tumors are relatively hypocellular and comprised of bland-appearing fibroblastic/myofibroblastic spindle cells arranged in fascicles parallel to the epidermis within a collagenous stroma. Tumors are usually confined to the dermis but may rarely show focal involvement of the superficial subcutaneous fat (Fig. 4.15a). No significant cytologic atypia, mitotic activity, or necrosis is present (Fig. 4.15b). Tumor cells in early lesions express SMA, but older lesions are negative for this marker, as well as S100 protein, desmin, and CD34. Elastic stains often demonstrates increased numbers of fibers (Table 4.15).

Differential Diagnosis

The primary differential diagnosis is with fibroblastic connective tissue nevus, but other entities in the differential include fibrous histiocytoma, leiomyoma, dermatofibrosarcoma protuberans,

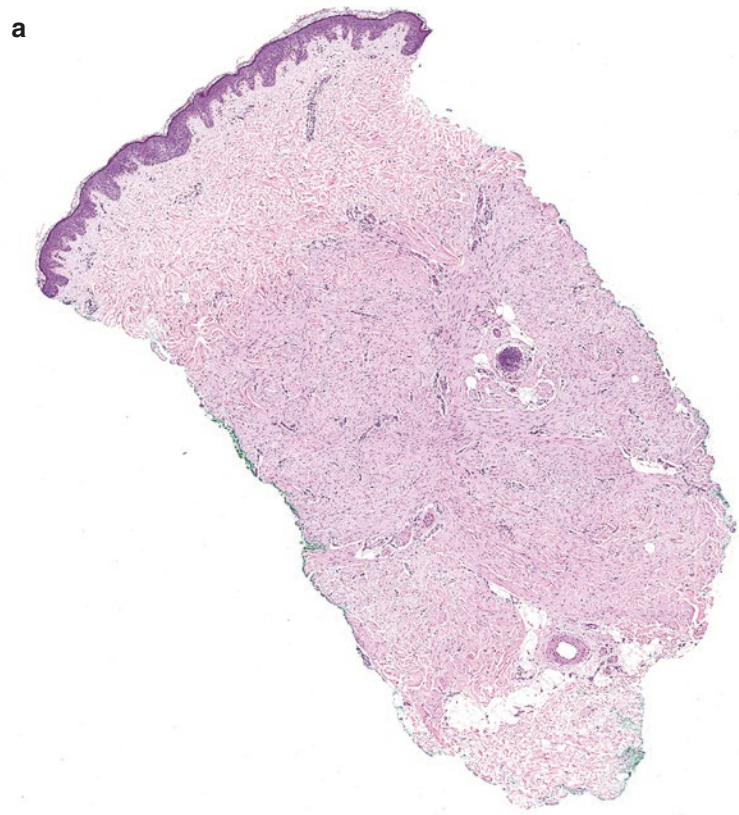


Fig. 4.15 Dermatomyofibroma. (**a**) A dermal-based, fibroblastic/myofibroblastic spindle cell proliferation arranged in horizontal fascicles (parallel to the epidermis) within a collagenous stroma. (**b**) The bland fibroblastic and myofibroblastic cells are devoid of atypia, mitoses, and necrosis

Fig. 4.15 (continued)

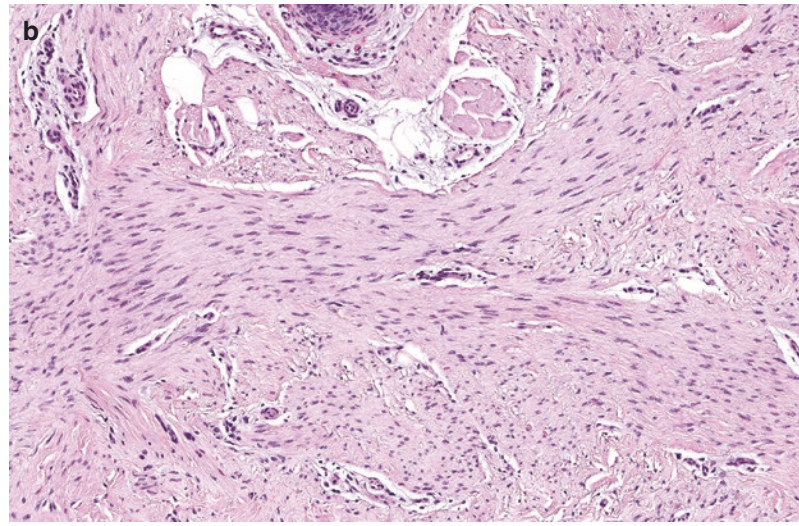


Table 4.15 Key pathologic features: dermatomyofibroma

Hypocellular lesion of bland-appearing fibroblastic/myofibroblastic spindle cells in fascicles parallel to the epidermis
Collagenous stroma
Rarely and only focally involves the subcutis
No atypia, mitoses, or necrosis
Only early lesions positive for SMA

fibrous hamartoma of infancy, superficial fibromatosis, and hypertrophic scar. Fibroblastic connective tissue nevus has shorter fascicles of spindle cells, often in association with collections of adipocytes in the reticular dermis, epidermal papillomatous hyperplasia, and usually CD34 expression. In some cases, the distinction can be very difficult but is of little consequence. Benign fibrous histiocytoma lacks the parallel fascicular pattern and demonstrates collagen trapping. Leiomyoma has an intersecting fascicular pattern of spindle cells with abundant eosinophilic cytoplasm, blunt-ended nuclei with perinuclear vacuoles, and SMA positivity. Dermatofibrosarcoma protuberans has a tight storiform proliferation of spindle cells and broad "honeycomb" infiltration of the subcutis. Unlike dermatomyofibroma, fibrous hamartoma arises in infants and young children and demonstrates triphasic histomorphology with immature mesenchymal spindle cells and bands of fibrocollagenous tissue and adipose tissue. Superficial fibromatoses are multinodular and hypercellular and lack the parallel arrangement of spindle cells. Hypertrophic scars have effacement of the rete pegs in the overlying epidermis, more conspicuous vertically oriented blood vessels, and may contain keloidal collagen.

Fibroblastic Connective Tissue Nevus

Clinical Features

Fibroblastic connective tissue nevus (FCTN) most commonly presents in children but can affect a wide age range, including middle-aged adults. Women are affected about twice as commonly as men. Lesions typically present as a plaque involving the trunk, extremities, or head and neck. Agminate and congenital cases have been reported. FCTN is a benign lesion without risk of recurrence or metastasis, even in cases with positive margins.

Pathologic Features

The overlying epidermis is papillomatous in the majority of cases (Fig. 4.16a). FCTN is poorly circumscribed and comprised of short intersecting fascicles of bland fibroblastic/myofibroblastic spindle cells present primarily in the reticular

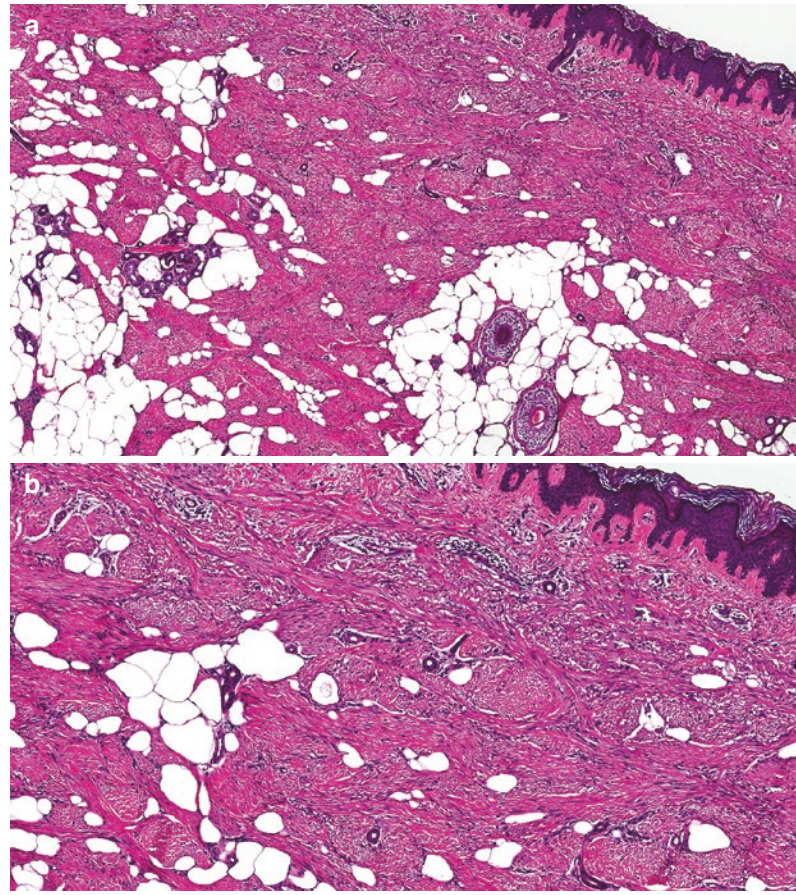


Fig. 4.16 Fibroblastic connective tissue nevus. (**a**) Papillomatous epidermis with underlying poorly circumscribed reticular dermal spindle cell proliferation that infiltrates into the subcutis. (**b**) The spindle cell proliferation is composed of short intersecting fascicles of bland fibroblastic/myofibroblastic cells present primarily in the reticular dermis. Note also collections of adipocytes within the reticular dermis

Table 4.16 Key pathologic features: fibroblastic connective tissue nevus

Poorly circumscribed lesion of short fascicles of bland fibroblastic/myofibroblastic spindle cells in the reticular dermis
Adipocytes within the reticular dermis
Frequent extension into the subcutis
No significant mitotic activity or cytologic atypia
CD34-positive, focal SMA immunoreactivity in half of cases, and negative for S100 protein and desmin

dermis with frequent extension into the subcutis (Fig. 4.16b). Collections of adipocytes within the reticular dermis are also present in the majority of cases. Mitotic activity and cytologic atypia are typically absent. By immunohistochemistry, most are CD34-positive and roughly half show some expression of SMA, while S100 and desmin are negative (Table 4.16).

Differential Diagnosis

FCTN has a broad differential diagnosis, the most important of which includes dermatomyofibroma, plaque-like CD34-positive dermal fibroma, pilar leiomyoma, dermatofibrosarcoma protuberans, and lipofibromatosis. The differentiating features of dermatomyofibroma are addressed above. Plaque-like CD34-positive dermal fibroma has a similar clinical presentation but typically has an atrophic rather than papillomatous epidermis. Also, the spindle cell proliferation of plaque-like CD34-positive dermal fibroma is usually restricted to the papillary and superficial reticular dermis, with vertical orientation of the spindle cells in the papillary dermis. Unlike in FCTN, collections of adipocytes in the reticular dermis are not a feature. Pilar leiomyoma is distinguished from FCTN by its dermal

proliferation of intersecting fascicles of spindle cells with abundant eosinophilic cytoplasm and cigar-shaped nuclei with perinuclear vacuoles. There is diffuse expression for SMA and variable desmin positivity. Dermatofibrosarcoma protuberans is composed of a tighter, more storiform proliferation of mildly atypical CD34-positive spindle cells involving the entire dermis and extending into the subcutis with a "honeycomb" pattern of infiltration. Lipofibromatosis has similar clinical features to FCTN but demonstrates biphasic histology consisting of spindle cells arranged in fascicles and with abundant adipose tissue infiltrating through skeletal muscle.

Superficial Fibromatoses

Clinical Features

Fibromatoses are a large group of benign, though sometimes locally aggressive, soft tissue tumors that occur across a wide age spectrum. In general, fibromatoses are subdivided into superficial (fascial) and deep types. Superficial fibromatoses usually occur in older adults without gender predilection and present as a slowly enlarging, multinodular soft tissue mass of the hands, feet, or penis. Palmar and plantar fibromatoses are also known as Dupuytren contracture and Ledderhose disease, respectively, while penile fibromatosis is also known as Peyronie disease. They have an autosomal dominant inheritance pattern with incomplete penetrance. While superficial fibromatoses have a benign clinical course, local recurrences after surgical excision are common, and other nonsurgical approaches may show variable efficacy. In contrast to superficial fibromatoses, deep fibromatoses (also known as desmoid-type fibromatoses) usually occur in younger adults and present as a slow-growing deep soft tissue mass in the extremities or trunk or intra-abdominally. In addition, a subset of patients with intra-abdominal deep fibromatoses may have familial adenomatous polyposis (FAP) syndrome and, thus, manifest other syndromic features, including intestinal polyposis, osteomas, and Gardner-associated fibromas (Gardner syndrome). In general, deep fibromatoses may show a more aggressive clinical course, with frequent local recurrences after surgical excision and occasional deaths despite multimodal therapeutic approaches (i.e., systemic chemotherapy, radiation therapy, etc.). There is an increasing trend for avoiding surgery unless medically necessary.

Pathologic Features

Superficial fibromatoses are multinodular, unencapsulated, but relatively circumscribed tumors (Fig. 4.17a). Deep fibromatoses are often poorly circumscribed and demonstrate prominent local infiltration of adjacent soft tissue and/or visceral organs. Microscopically, fibromatoses are variably cellular and comprised predominantly of bland-appearing fibroblasts/myofibroblasts with scant eosinophilic to amphophilic cytoplasm, tapered vesicular nuclei that have undulating nuclear membranes, and inconspicuous nucleoli. Tumor cells are arranged in long, intersecting fascicles within a collagenous stroma containing thin-walled curvilinear vessels with frequent associated mild perivascular lymphocytic inflammation and edema (Fig. 4.17b). Plantar fibromatoses, particularly those in younger patients, may be relatively hypercellular, with focally increased cytologic atypia, scattered multinucleated cells, and/or mitotic activity (Fig. 4.17c and d). In contrast, a subset of superficial fibromatoses, particularly those involving the hands or penis, may be relatively hypocellular with hyalinized stroma (Fig. 4.17e). Tumor cells typically express smooth muscle and/or muscle-specific actin and are negative for S100 protein, CD34, desmin, and pan-cytokeratin expression. Sporadic deep fibromatoses show recurrent somatic activating *CTNNB1* mutations, whereas FAP-associated deep fibromatoses demonstrate inactivating *APC* mutations with somatic loss of heterozygosity; as such, beta-catenin immunostains usually show strong and diffuse nuclear accumulation in deep fibromatoses. Nuclear positivity for beta-catenin is seen in approximately 50% of superficial fibromatoses and is typically focal. Gains of whole

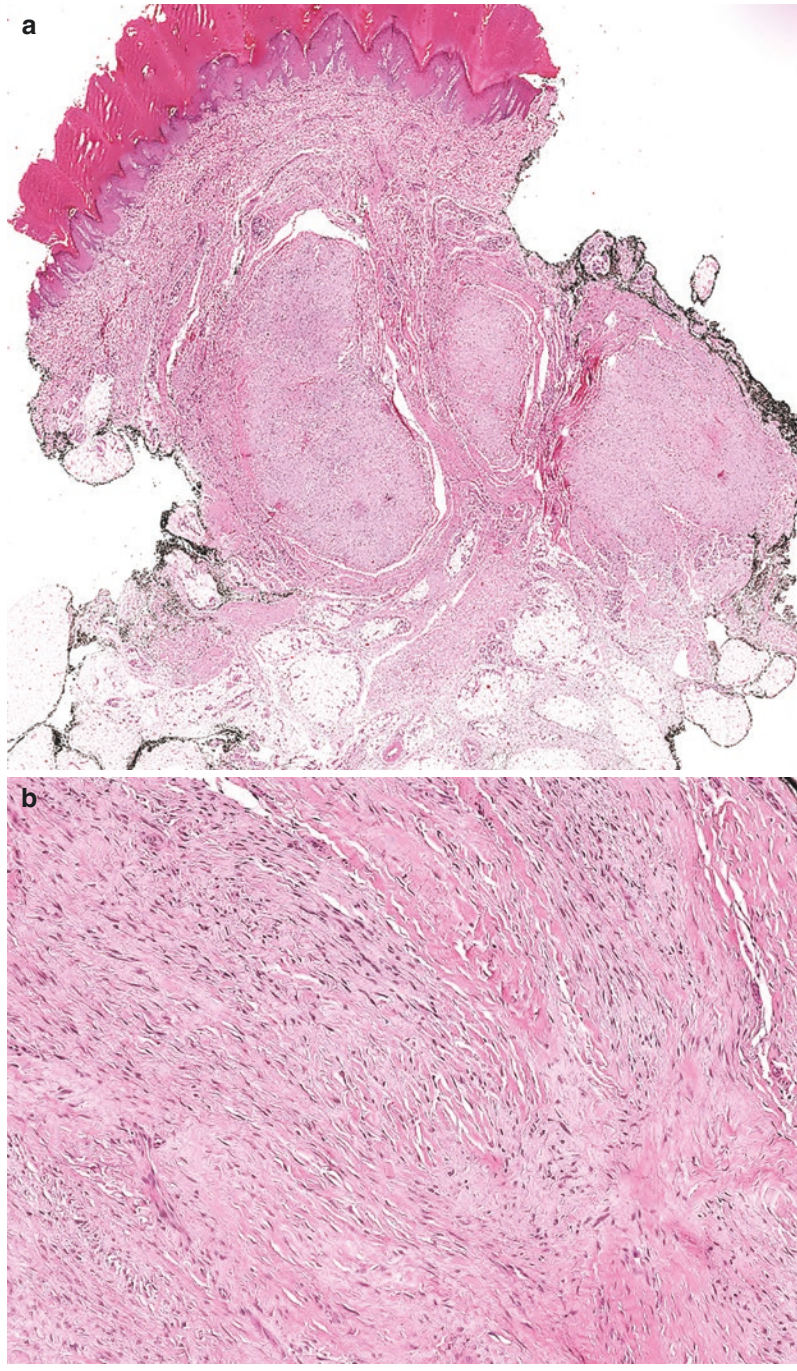
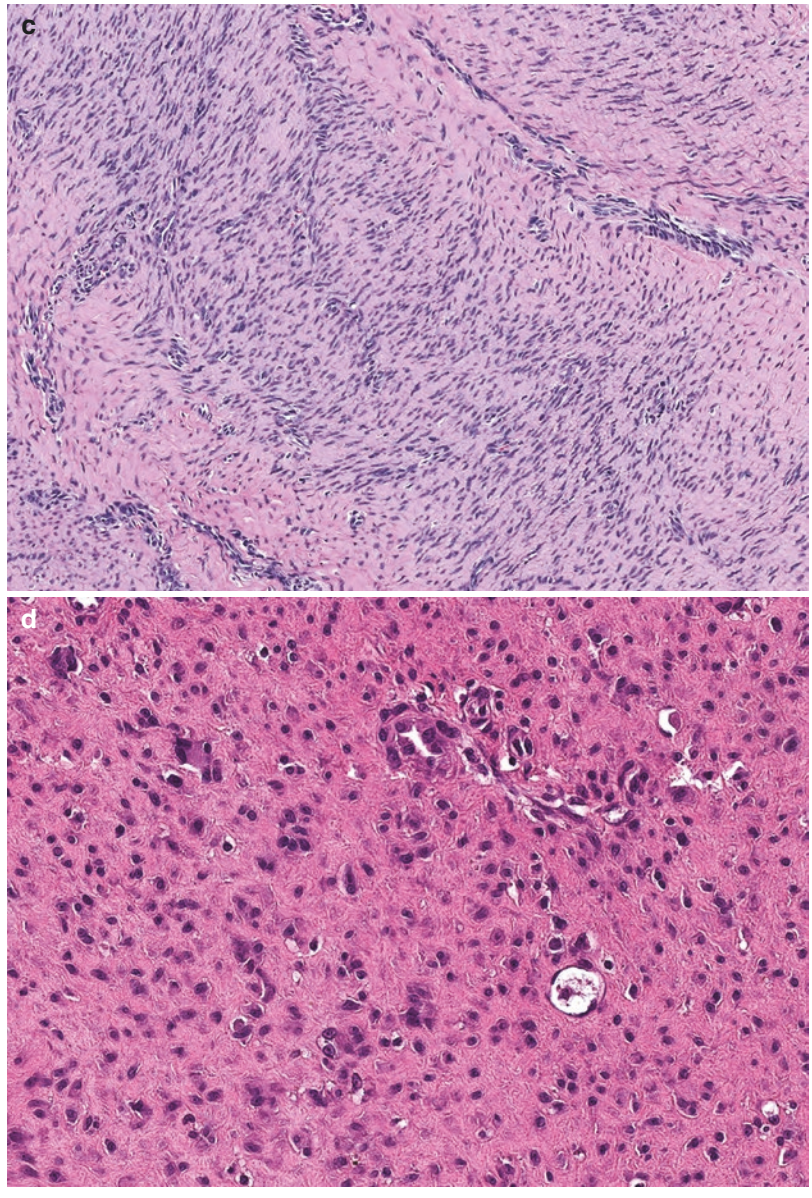


Fig. 4.17 Superficial fibromatoses. (**a**) Tumors are multinodular, unencapsulated, but relatively circumscribed. (**b**) An example of palmar fibromatosis composed of a variably cellular proliferation of bland-appearing fibroblastic spindle cells arranged in long, intersecting fascicles set within a collagenous stroma. (**c**) Some cases, particularly plantar fibromatosis in younger patients, may be somewhat more cellular. Thin-walled vessels with mild perivascular inflammation are noted in both **b** and **c**. (**d**) Multinucleated cells are relatively common in plantar fibromatosis. (**e**) Some cases, particularly those involving the penis, may be hypocellular

Fig. 4.17 (continued)



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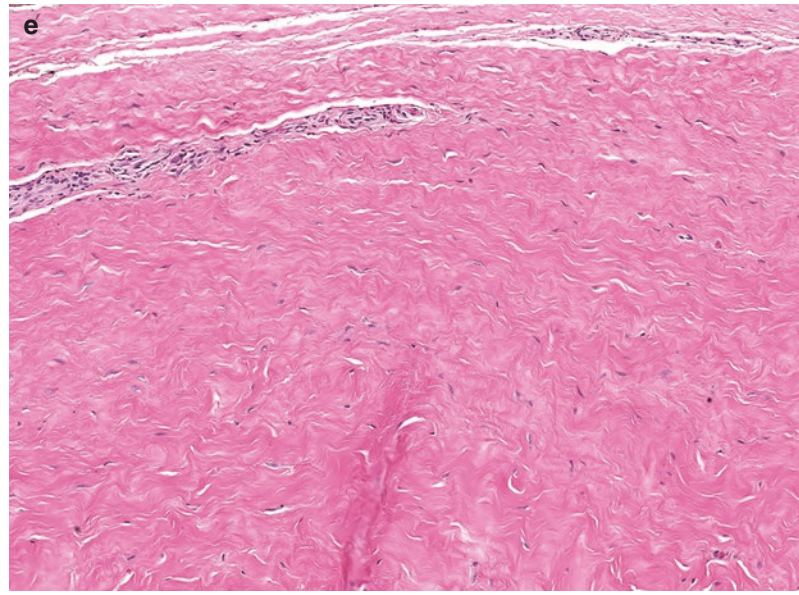


chromosomes 7 and 8 are seen in palmar fibromatoses, and gains of 8 and 14 are present in plantar fibromatoses. Palmar fibromatoses may also demonstrate abnormalities involving 14q11.2 and 7p14.1 (Table 4.17).

Differential Diagnosis

The primary differential diagnosis of superficial fibromatosis is with fibroma of tendon sheath. Fibroma of tendon sheath is typically less cellular and lacks the fascicular growth pattern of fibromatosis. Cellular examples of fibroma of tendon sheath do not have long fascicles, as discussed above. Calcifying aponeurotic fibromas also present in acral surfaces, but have distinct calcified and chondroid areas. Dermatomyofibroma and fibroblastic connective tissue nevus do not typically involve acral sites or the penis and are primarily located in the dermis. Both superficial acral and deep (desmoid) fibromatoses do not typically involve the dermis. Cellular fibrous histiocytoma has a central fascicular growth pattern

Table 4.17 Key pathologic features: superficial fibromatoses

Long fascicles of fibroblasts and myofibroblasts in a collagenous stroma
Focally SMA and muscle-specific actin-positive, nuclear beta-catenin positive in 50% of cases (focal)
Palmar fibromatosis (Dupuytren contracture)
Relatively hypocellular
Gains of whole chromosomes 7 and 8 and abnormalities involving 14q11.2 and 7p14.1
Plantar fibromatosis (Ledderhose disease)
Relatively hypercellular, especially in younger patients
Focal increased cytologic atypia, multinucleated cells, and/or mitoses
Gains of whole chromosomes 8 and 14
Penile fibromatosis (Peyronie disease)
Relatively hypocellular with prominent hyalinized stroma
Key pathologic features: deep fibromatoses
Same histologic features as with superficial fibromatosis
May have variable stromal myxoid change
Somatic cases with activating *CTNNB1* mutations, FAP-associated cases with inactivating *APC* mutations
Nuclear beta-catenin diffusely present in most cases

resembling fibromatosis, but the peripheries show typical features of conventional fibrous histiocytoma, such as storiform growth and peripheral collagen trapping. Synovial sarcoma can present in the peripheral extremities, but unlike fibromatosis is composed of plumper spindle cells with overlapping nuclei, often has a staghorn vasculature, is positive for TLE, is usually focally positive for cytokeratins, and has a t(X;18).

Juvenile Hyaline Fibromatosis

Clinical Features

Juvenile hyaline fibromatosis (JHF), also known as fibromatosis hyalinica multiplex juvenilis and Murray-Puretic-Drescher syndrome, is a rare autosomal recessive genodermatosis with variable penetrance, that is characterized by hyalinizing fibrosis of the skin and internal organs. Approximately 70 cases have been reported to date. Patients typically present in early childhood, usually during the first 2 years of life, with multiple papular skin lesions, gingival hyperplasia, joint contractures, and osteolytic bone lesions. Males are affected slightly more than females. Clinically, skin lesions may resemble an adnexal neoplasm or non-melanoma skin cancer. The systemic variant of JHF is known as infantile systemic hyalinosis (ISH) and has an earlier onset and poor prognosis. Hyaline fibromatosis syndrome (HFS) has been suggested as a unifying descriptor to include patients with either JHF or ISH. Treatment of JHF usually involves multiple resections of cutaneous nodules, due to a high recurrence rate. Radiotherapy is ineffective. Intralesional steroid injection may reduce the size of lesions. In patients with ISH, gingivectomy can help improve nourishment, and penicillamine has been reported to improve joint mobility. Nonetheless, the prognosis for ISH is poor with most patients dying of malnutrition, infection, or intractable diarrhea before the age of 2.

Pathologic Features

Microscopy shows skin lesions to be composed of bland spindle-shaped fibroblastic cells embedded within a PAS/Alcian blue-positive, Congo red-negative, densely hyalinized stroma (Fig. 4.18a and b). Elastic tissue is not present. Early lesions are more cellular than older lesions (Fig. 4.18c). Some cases may contain spherical calcified particles resembling psammoma bodies. By immunohistochemistry spindle cells are negative for SMA, and there is a population of CD68-positive macrophages in between the spindle cells. Loss-of-function mutations in capillary morphogenesis gene 2 (*CMG2/ANTXR2*), a transmembrane surface protein, result in accumulation of collagen IV in the extracellular matrix, which leads to the manifestations of HFS (Table 4.18).

Differential Diagnosis

Due to the deposition of amorphous material, cutaneous lesions of HFS may clinically and histopathologically resemble lipoid proteinosis, amyloidosis, scleromyxedema, or myofibroma. Lipoid proteinosis is a rare autosomal recessive genodermatosis caused by a loss-of-function mutation or reduced expression of the gene encoding extracellular matrix protein 1 (ECM1) on chromosome 1q21. This leads to the deposition of hyaline material within the skin and submucosa, which manifests as the pathognomonic dermatologic finding of this disorder, beaded papules over the lid margins termed "moniliform blepharosis." These features distinguish this disorder from HFS. Amyloidosis demonstrates apple-green birefringence on Congo red staining, which is not seen in HFS. Unlike HFS, scleromyxedema is a chronic fibromucinous disorder characterized by monoclonal gammopathy and generalized papular and sclerodermoid skin lesions, which by histology demonstrate dermal mucin, increased collagen deposition, and a proliferation of fibroblasts. Myofibromas are not hyalinized like

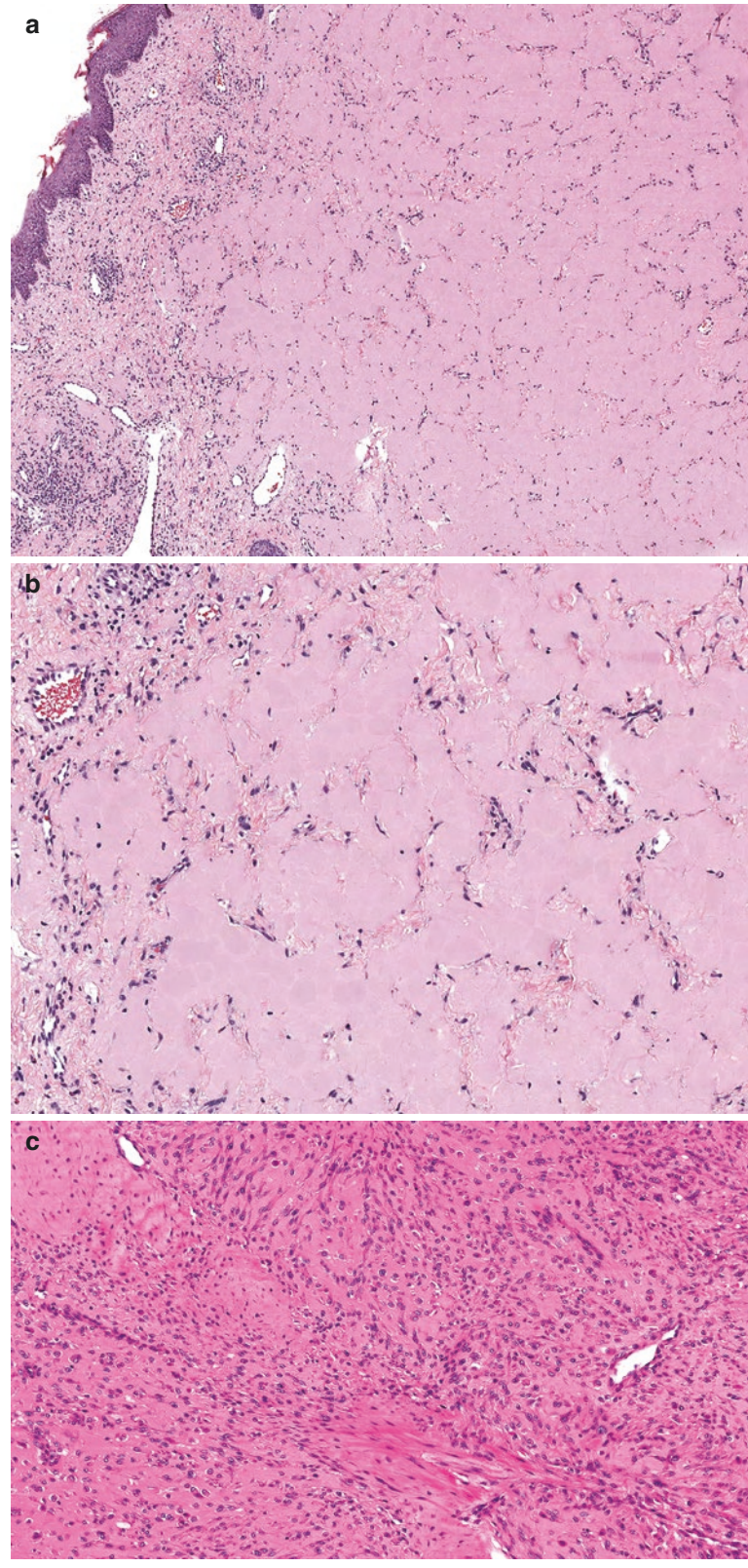


Fig. 4.18 Juvenile hyaline fibromatosis. (**a**, **b**) A skin lesion of juvenile hyaline fibromatosis composed of bland spindle-shaped fibroblastic cells embedded within a densely hyalinized stroma. (**c**) Early lesions of juvenile hyaline fibromatosis are more cellular, as in this case

Table 4.18 Key histopathologic features: juvenile hyaline fibromatosis/infantile systemic hyalinosis/hyaline fibromatosis syndrome

Bland spindle-shaped fibroblastic cells within PAS/Alcian blue-positive, densely hyalinized stroma
Early lesions more cellular than older ones
May contain spherical calcified particles resembling psammoma bodies
Spindle cells negative for SMA
Population of CD68-positive macrophages in between spindle cells
Loss-of-function mutations in capillary morphogenesis gene 2 (*CMG2/ANTXR2*) result in accumulation of collagen IV in the extracellular matrix

lesions of HFS, but instead are composed of a well-circumscribed, paucicellular proliferation of SMA-positive, desmin-negative "myoid" spindle cells in association with a prominent hemangiopericytomatous (staghorn) vasculature.

Infantile Fibromatosis (Lipofibromatosis)

Clinical Features

Two distinct morphological types of fibromatosis occurring in infancy and childhood have been described. The first is extremely rare, essentially identical to adult desmoid fibromatosis, and will not be discussed further. The other variant, also called lipofibromatosis or mesenchymal-type infantile fibromatosis, is an uncommon benign soft tissue tumor with slight male predominance that typically occurs in infants and children, including a small subset of congenital cases. Tumors usually present as a rapidly enlarging deep soft tissue mass in the extremities, thorax, abdomen, or head and neck and may recur locally after incomplete surgical excision. These lesions, however, do not metastasize.

Pathologic Features

Lipofibromatosis is a poorly circumscribed, hypercellular tumor comprised predominantly of bland-appearing round-to-ovoid cells with a moderate amount of eosinophilic cytoplasm, enlarged and slightly irregular nuclei, and inconspicuous nucleoli. Tumor cells are arranged haphazardly or form small bundles and fascicles within a fibromyxoid stroma and show a characteristic diffuse, infiltrative growth into adjacent soft tissue, including adipose tissue and skeletal muscle (Fig. 4.19a). Some of the smaller fat cells (adipocytes) observed in these lesions are likely a result of fatty proliferation due to muscular atrophy secondary to tumor infiltration of skeletal muscle (Fig. 4.19b). Although mitotic activity and cellularity may be focally increased, cytologic atypia is minimal, and necrosis is absent. Tumor cells typically express smooth muscle and/or muscle-specific actin and are negative for S100, CD34, desmin, and pan-cytokeratin. No recurrent genetic abnormalities have been described, but a case with a three-way t(4;9;6) has been reported (Table 4.19).

Differential Diagnosis

The major differential diagnosis for infantile fibromatosis (lipofibromatosis) is with infantile (congenital) fibrosarcoma. Despite the possibility of significant morphologic and immunophenotypic overlap, cellular infantile fibromatosis (lipofibromatosis) can typically be distinguished from infantile (congenital) fibrosarcoma by its lack of a herringbone growth pattern. Additionally, a diffuse infiltrative pattern and variation in cellularity is suggestive of lipofibromatosis, while uniform hypercellularity, marked mitotic activity, and/or necrosis favor a diagnosis of infantile (congenital) fibrosarcoma. In difficult cases, demonstration of the *ETV6-NTRK3* gene fusion of infantile fibrosarcoma rules out lipofibromatosis. Interestingly, a group of superficial soft tissue tumors occurring in children and young adults reminiscent of lipofibromatosis, with variable cytologic atypia and a distinct immunophenotype of S100 protein and CD34 positivity suggestive of neural differentiation and recurrent gene fusions involving the *NTRK1* gene, has been recently reported. The relationship, if any, of these to lipofibromatosis remains to be determined. Lipofibromatosis demonstrates infiltrative growth into adipose tissue mimicking the growth

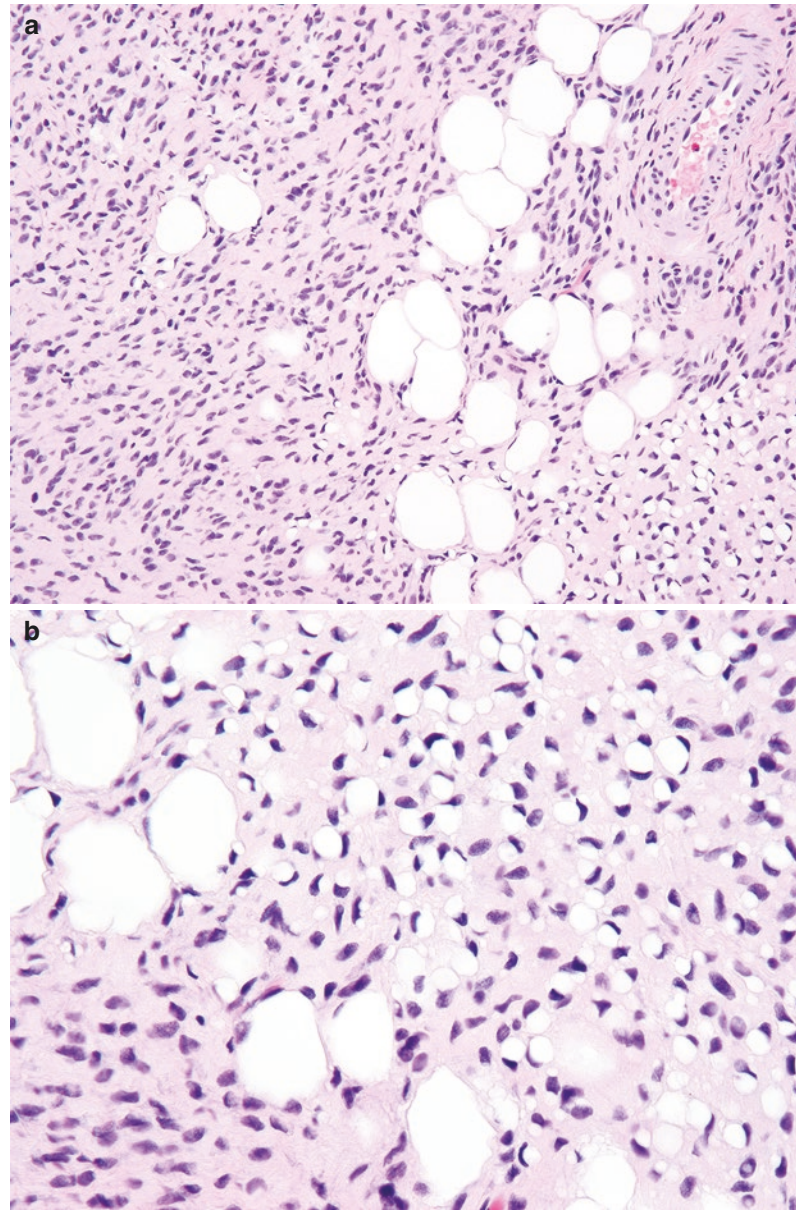


Fig. 4.19 Infantile fibromatosis (lipofibromatosis). (**a**) A poorly circumscribed, hypercellular tumor comprised of bland-appearing round-to-ovoid cells arranged haphazardly or forming small bundles and fascicles within a fibromyxoid stroma. (**b**) A case with more prominent small lipocytes. These cells are likely due to fatty proliferation in response to muscular atrophy secondary to tumor infiltration of skeletal muscle. (Images courtesy of Dr. Andrew Folpe, Mayo Clinic)

Table 4.19 Key pathologic features: infantile fibromatosis (lipofibromatosis)

Poorly circumscribed tumor with haphazardly arranged fibroblast-like or primitive mesenchymal cells in a myxoid stroma
Prominent infiltration into skeletal muscle and adipose tissue
Proliferation of lipocytes secondary to skeletal muscle atrophy may be extensive
Mitotically active cellular spindle cell areas with fascicular growth resemble infantile fibrosarcoma
Variable staining for smooth muscle and muscle-specific actin, desmin typically negative

pattern seen in DFSP and diffuse neurofibroma. DFSP has a predominantly storiform growth pattern, is diffusely CD34-positive, and has a *COL1A1-PDGFRB* fusion, features not seen in lipofibromatosis. The infiltration of adipose tissue by lipofibromatosis may also lead to consideration of a lipogenic tumor such as myxoid liposarcoma or lipoblastoma. Myxoid liposarcoma is vanishingly rare in infants and children, has a distinctive "chicken-wire" vascular pattern, and has *DDIT3* translocation, which can be dem-

onstrated by FISH. Lipoblastoma is more myxoid with a prominent lobular growth pattern and uniformity in the size of adipocytes, unlike lipofibromatosis.

Benign Fibrous Histiocytoma (Dermatofibroma)

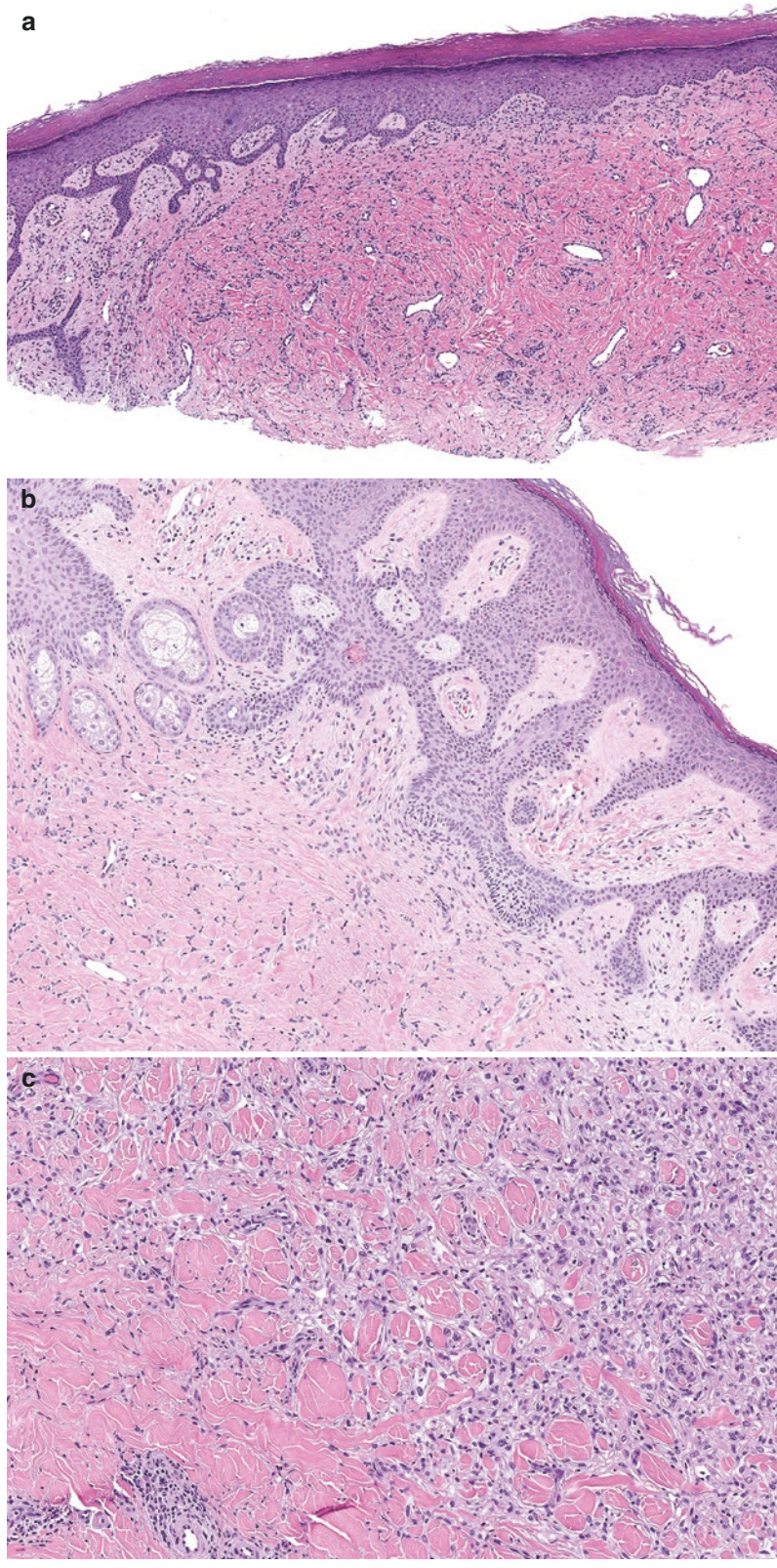
Clinical Features

Benign fibrous histiocytoma (dermatofibroma) encompasses a family of benign tumors with overlapping clinical and histologic features. They are usually ≥1 cm in diameter, but may reach up to 10 cm in size, and involve the extremities of young-to-middle-aged adults (but may occur at any age). They often present as a superficial, slow-growing papulonodular lesion with variably increased pigmentation. Conventional fibrous histiocytoma/dermatofibroma is more common in younger women and has a propensity to arise on the legs. Other variants have a largely equal sex distribution. Occasional lesions may arise in the arms, trunk, and distal extremities. Involvement of the head and neck and face is uncommon, except for the cellular variant. Rare cases may be multiple and distributed widely or agminated and arise in the deep dermis or subcutis and can be quite large. In general, these tumors demonstrate indolent behavior with a low risk of local recurrence. Certain histologic types (those involving the face, cellular, aneurysmal/hemosiderotic, deep, and atypical variants) are associated with an increased risk of local recurrence (up to 20% in some series). Exceptionally, metastases and even death from disease have been reported and, similar to the increased risk for local recurrence, are also associated with the aforementioned histologic subtypes. It should be stressed that metastasis and death are so rare that all of the members of this group are still best regarded as benign entities, with some risk for local nondestructive recurrence. Simple excision is curative in most cases. In general, we recommend conservative re-excision of the subtypes at increased risk for recurrence with due consideration for cosmetically sensitive locations.

Pathologic Features

All members of this group share certain histopathologic features, including relative circumscription, origin in the reticular dermis, and frequent overlying epidermal hyperplasia with increased basilar pigmentation (Fig. 4.20a). Occasional cases will show follicular or sebaceous induction in the overlying epidermis (Fig. 4.20b). Cases in the deeper dermis or subcutis usually lack overlying epidermal change and are larger. At the periphery of the tumor, the constituent spindle cells will interdigitate with peripheral collagen fibers of the reticular dermis, so-called collagen trapping (Fig. 4.20c). For larger or more deeply situated tumors, involve-

Fig. 4.20 Benign fibrous histiocytoma (dermatofibroma). (**a**) Circumscribed dermal proliferation with epidermal hyperplasia. (**b**) Occasional cases may show follicular or sebaceous induction. (**c**) Peripheral collagen trapping. (**d**) Extension into subcutaneous fat with fat necrosis and inflammation. (**e**) Conventional benign fibrous histiocytoma with spindle cells in vaguely storiform arrangement (bottom) and siderophages, histiocytes, Touton-like giant cells, and scattered small lymphocytes (top). (**f**) The lipidized (ankle-type) variant tends to be hypocellular with foamy histiocytes in a hyalinized background. (**g**) The cellular variant has intersecting fascicles of tumor cells with little to no secondary elements and may demonstrate necrosis in up to 10% of cases. Cytologic atypia and atypical mitoses will be absent, assuaging the concern for malignancy. (**h**) Aneurysmal and/or hemosiderotic variant with hemorrhagic pseudovascular spaces and siderophages. (**i**) Atypical fibrous histiocytoma demonstrating admixed hyperchromatic, pleomorphic, and multinucleated cells. Other features of conventional dermatofibroma such as collagen trapping (seen here) allow distinction from atypical fibroxanthoma/pleomorphic dermal sarcoma and undifferentiated pleomorphic sarcomas. (**j**) Deep benign fibrous histiocytoma demonstrating a prominent staghorn (hemangiopericytomatous) vasculature. (**k**) Granular cell variant containing plump spindled-to-ovoid cells with abundant eosinophilic granular cytoplasm. (**l**) A rare myxoid example of benign fibrous histiocytoma. (**m**) Keloidal variant of benign fibrous histiocytoma. (Image courtesy of Dr. Thomas Brenn, University of Calgary). (**n**) CD34 is generally negative, but can be positive at the periphery of benign fibrous histiocytomas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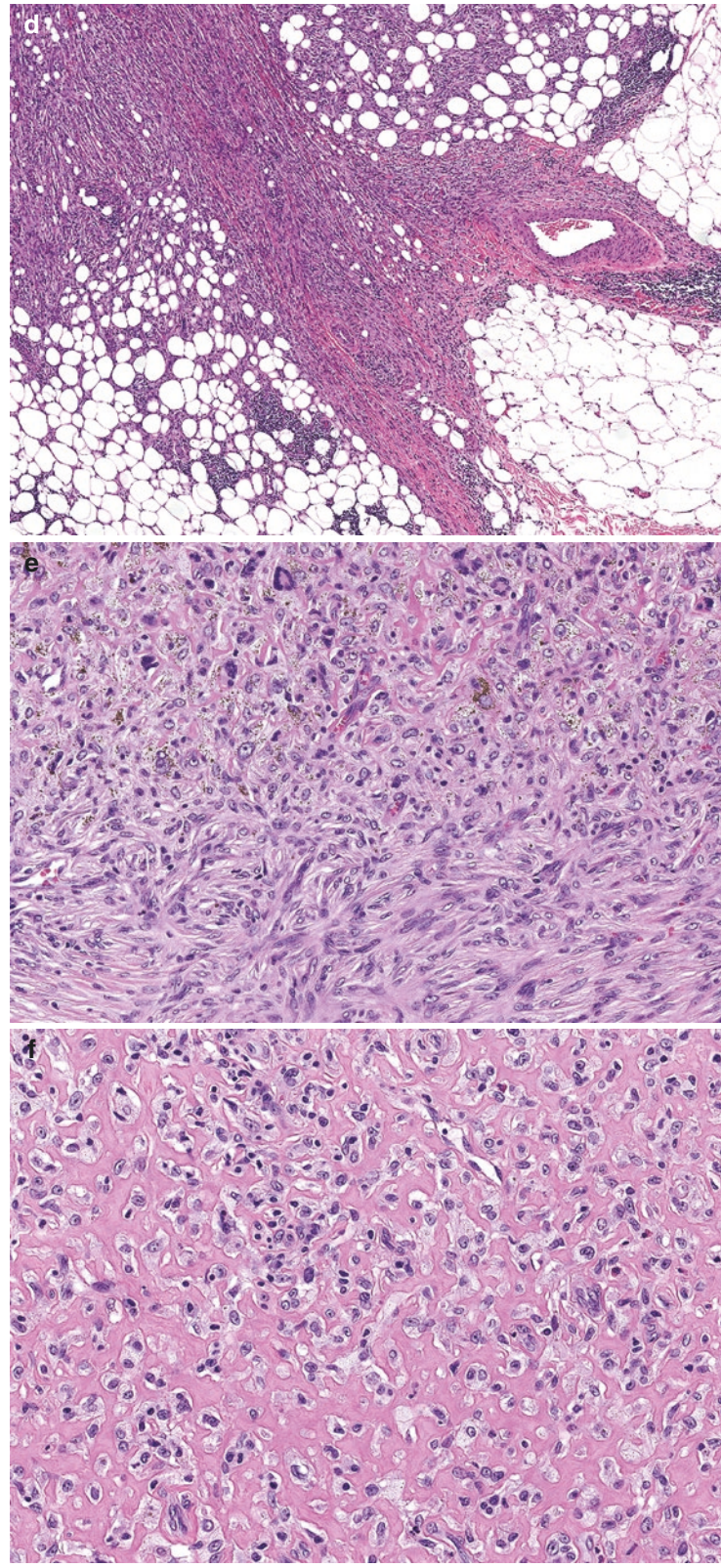

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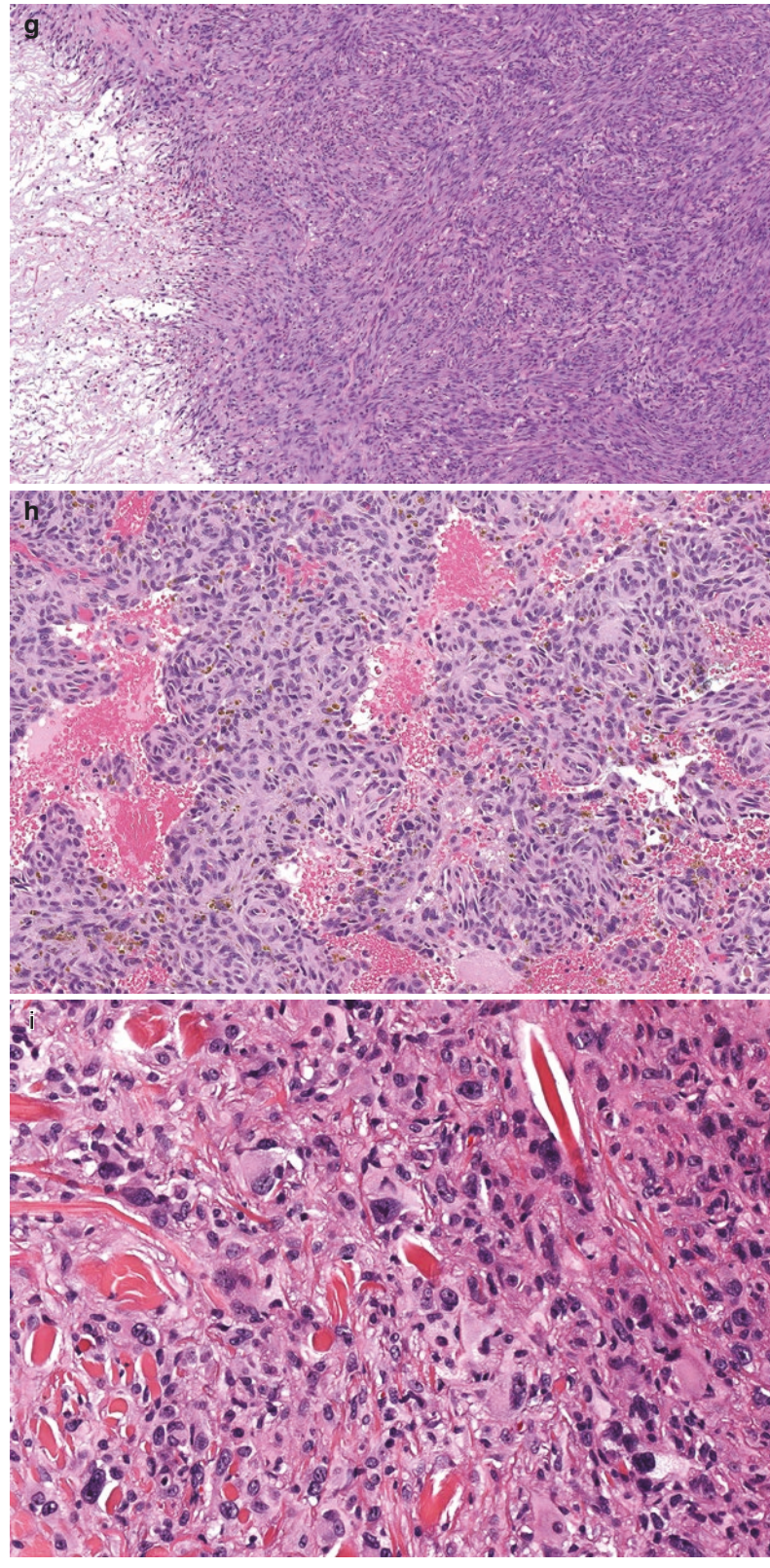

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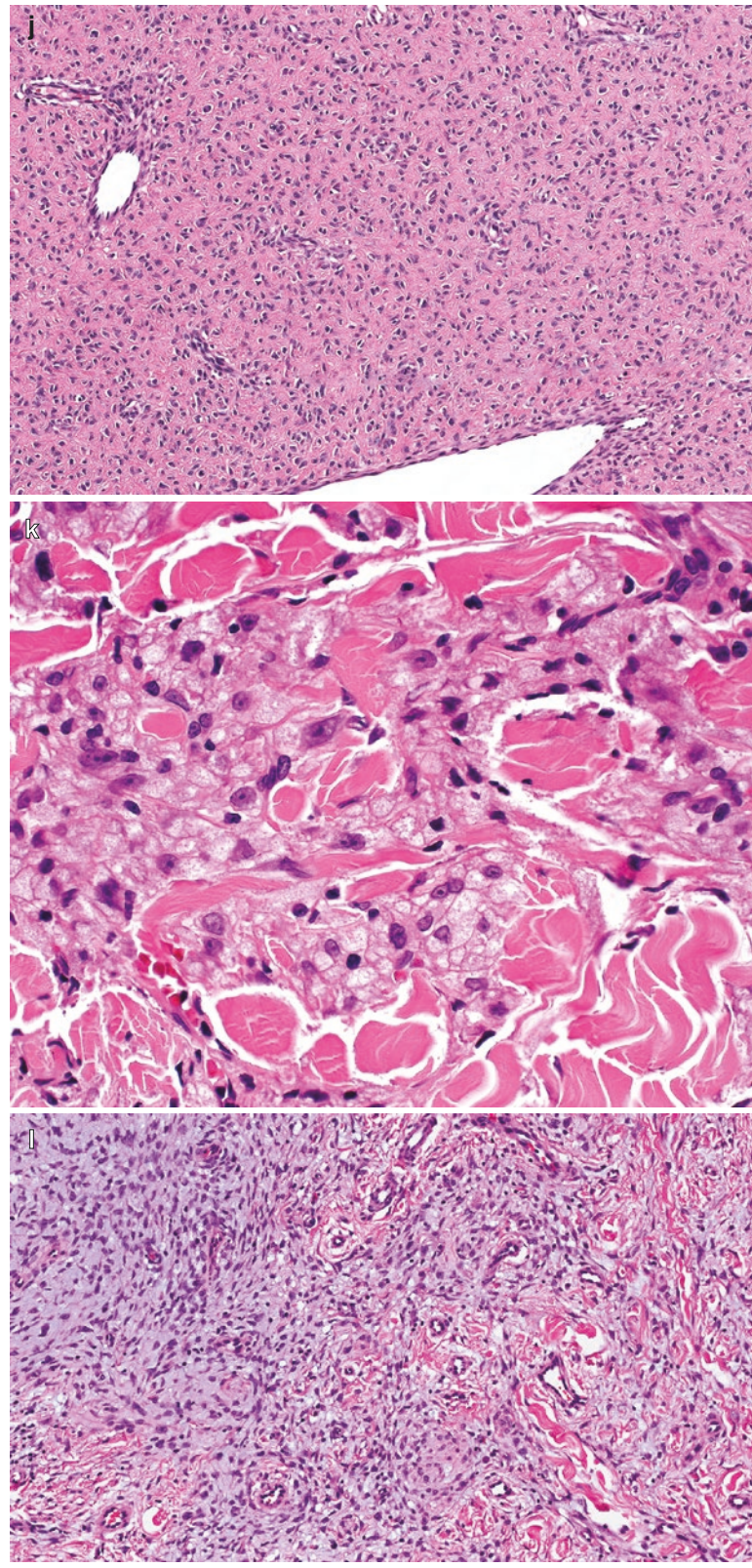

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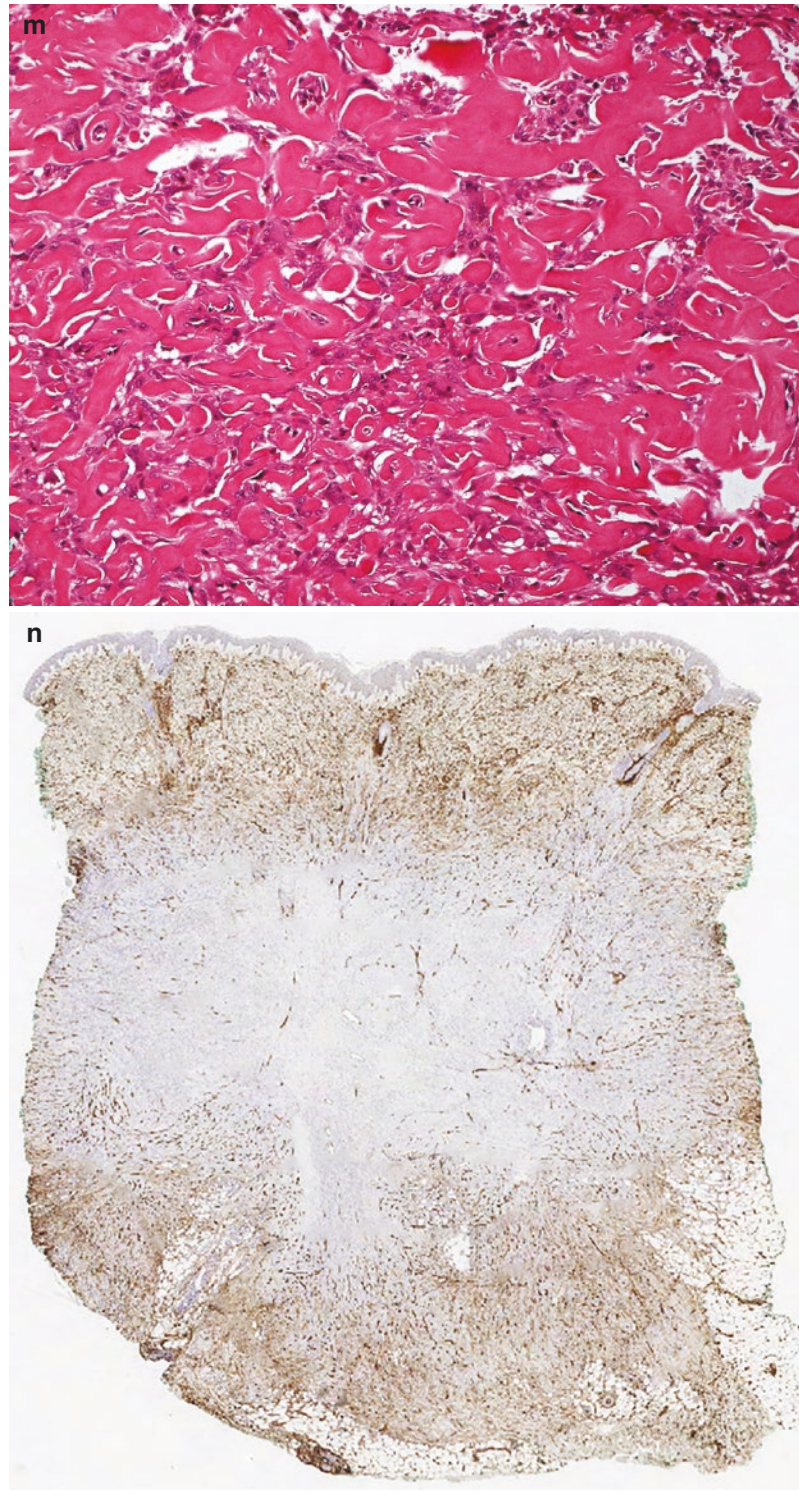


ment of the subcutis is common. Infiltration into the subcutis occurs in a limited, relatively circumscribed fashion along expanded fibrous septa. This infiltration is often associated with foci of fat necrosis and a lymphohistiocytic infiltrate (Fig. 4.20d). There are numerous histologic variants of DF. The distinguishing features of the most important subtypes are described below.

Conventional Benign Fibrous Histiocytoma/Dermatofibroma

Conventional benign fibrous histiocytoma/dermatofibroma is classically a polymorphous tumor composed of an admixture of bland, lightly eosinophilic spindle cells in a focally storiform growth pattern, fibroblasts, histiocytes, siderophages, multinucleated cells (including Touton-type giant cells), and scattered lymphocytes (Fig. 4.20e). The cellularity is variable. Burned-out cases may show fibrosis and relatively low cellularity.

Lipidized (Ankle-Type) Fibrous Histiocytoma

Lipidized (ankle-type) fibrous histiocytoma is very similar to a conventional dermatofibroma with the notable addition of numerous foamy histiocytes and background hyalinizing fibrosis (Fig. 4.20f). These lesions often tend to be somewhat hypocellular and are seen most commonly on the distal lower extremity, hence the alternative designation as "ankle-type" dermatofibromas.

Cellular Fibrous Histiocytoma

Cellular fibrous histiocytoma differs from the conventional form by its relative uniform cellularity and predominantly fascicular growth pattern. The tumor is composed of fascicles of uniform spindled cells with little to no secondary elements (i.e., admixed histiocytes and lymphocytes) (Fig. 4.20g). Mitotic activity is common (up to 5–10 mitoses/10 HPFs), but atypical mitotic figures are not seen. Necrosis may be seen in up to 10% of cases. The latter features may raise concern for malignancy. Approximately 20% of this subtype arise on the head and neck and face and account for approximately 80% of head and neck benign fibrous histiocytomas.

Aneurysmal and/or Hemosiderotic Fibrous Histiocytoma

Aneurysmal and/or hemosiderotic fibrous histiocytomas demonstrate varying amounts of intratumoral hemorrhage, typically consisting of large collections of blood in pseudocystic spaces not lined by endothelial cells in association with numerous siderophages (Fig. 4.20h). The background tumor can resemble a conventional benign fibrous histiocytoma, atypical fibrous histiocytoma (see below), or, frequently, cellular fibrous histiocytoma.

Atypical Fibrous Histiocytoma/ Dermatofibroma with Monster Cells

Atypical fibrous histiocytoma, also known as dermatofibroma with monster cells, resembles a conventional benign fibrous histiocytoma with admixed hyperchromatic, pleomorphic, and multinucleated cells (Fig. 4.20i). Mitotic figures may be seen, and in contrast to other fibrous histiocytomas, atypical forms may be present. Features of conventional dermatofibroma, such as collagen trapping and secondary elements, are also present allowing distinction from atypical fibroxanthoma/pleomorphic dermal sarcoma and undifferentiated pleomorphic sarcomas.

Deep Fibrous Histiocytoma

Deep fibrous histiocytomas arise in the deep dermis or subcutis, tend to be large, are less fibrous, are more cellular, and often have a prominent staghorn (hemangiopericytomatous) vasculature (Fig. 4.20j). In our experience, this variant and cellular fibrous histiocytoma are most often mistaken for a sarcoma.

Rare Variants

Rarely encountered variants include clear cell, granular cell (Fig. 4.20k), balloon cell, myxoid (Fig. 4.20l), and keloidal dermatofibroma (Fig. 4.20m).

Immunohistochemistry is rarely necessary for the diagnosis of benign fibrous histiocytomas. Classically, they are immunoreactive for FXIIIa and

Table 4.20 Key pathologic features: benign fibrous histiocytoma (dermatofibroma)

Conventional benign fibrous histiocytoma (dermatofibroma)
Varying amounts of epidermal hyperplasia, basal layer hyperpigmentation, and follicular induction
Circumscribed but unencapsulated tumor arising in the reticular dermis
Composed of bland lightly eosinophilic spindle cells present in a focally storiform growth pattern
Secondary elements including Touton-type giant cells, hemosiderin and foam-laden cells, and a lymphohistiocytic infiltrate
Peripheral collagen trapping
FXIIIa positive, variable immunoreactivity for SMA, CD68, and CD10. Negative for CD34, S100 (except in dendritic cells), and desmin
Lipidized fibrous histiocytoma
Tendency to arise in the lower extremity particularly around the ankle
Similar to conventional dermatofibroma with the addition of extensive hyalinizing fibrosis and numerous foamy histiocytes
Cellular fibrous histiocytoma
Cellular proliferation of uniform spindle cells in a fascicular growth pattern
Few if any secondary elements
Increased mitotic activity, but no atypical forms
Focal necrosis in up to 10% of cases
20% arise on the head, neck, or face
May have a peripheral rim of CD34-positive spindle cells
Aneurysmal and/or hemosiderotic fibrous histiocytoma
Varying amounts of intratumoral hemorrhage often contained within pseudocystic spaces
Abundant hemosiderin
Background tumor may be conventional, atypical, or cellular fibrous histiocytoma
Intratumoral hemorrhage may cause rapid clinical change in size and pigmentation raising concern for melanoma
Atypical fibrous histiocytoma/dermatofibroma with monster cells
Resembles conventional benign fibrous histiocytoma with varying numbers of hyperchromatic, pleomorphic, and multinucleated cells
Mitotic figures including atypical forms may be seen
Deep fibrous histiocytoma
Arises in the deep dermis or subcutis
Often large, less fibrous, and more cellular than typical fibrous histiocytoma
May have a prominent staghorn (hemangiopericytomatous) vasculature
Most common variant, in addition to cellular fibrous histiocytoma, to be mistaken for a sarcoma

negative for CD34. It should be mentioned that cellular fibrous histiocytoma is often negative for FXIIIa. It is also common for reactive CD34 cells to be present at the periphery of the tumor (Fig. 4.20n), leading to concern for DFSP. Unlike DFSP, the central portion of the tumor, with rare exceptions, is negative for CD34 in lesional cells. Variable immunoreactivity for SMA, CD68, CD163, and CD10 is common. Immunohistochemical stains for S100 protein are negative, but entrapped dendritic cells are frequently highlighted with this stain. Dermatofibromas are negative for desmin and cytokeratins. It should be stressed that histologic features rather than immunohistochemical stains should be the basis for diagnosis. We rarely order immunohistochemical stains for this group of tumors.

Previously it has been suggested that dermatofibromas represent a reactive process due to the fact that a subset are associated with arthropod bites, trauma, or folliculitis. However, molecular studies have demonstrated clonality, chromosomal copy number gains and losses, and gene fusions involving a number of different loci, including protein kinase C genes, *PRKCB* and *PRKCD*, as well *LAMTOR1*, and genes for CD63 and podoplanin. These genetic findings support the interpretation that this group of tumors represents true neoplasms, rather than reactive proliferations (Table 4.20).

Differential Diagnosis

The primary differential diagnosis for conventional benign fibrous histiocytoma and the cellular variant is dermatofibrosarcoma protuberans. Dermatofibrosarcoma protuberans (DFSP) lacks the overlying epidermal changes, has little to no collagen trapping, and usually demonstrates diffuse infiltration into the subcutaneous fat in the absence of fat necrosis and inflammation. DFSP is more monomorphic than conventional benign fibrous histiocytoma and has a tighter storiform growth pattern and more slender, hyperchromatic nuclei than are seen in cellular fibrous histiocytoma. DFSP is diffusely positive for CD34 with only focal immunoreactivity for FXIIa and has a *COL1A1-PDGFRB* fusion.

Hypocellular examples of conventional benign fibrous histiocytoma can be confused with sclerotic blue nevus, neurofibroma, and sclerosing perineurioma. In sclerotic blue nevi, the pigmented cells contain melanin rather than hemosiderin. Neurofibromas produce their own more delicate "shredded carrot" collagen, whereas the spindle cells of benign fibrous histiocytomas intercalate between pre-existing reticular dermal collagen bundles. Both blue nevus and neurofibroma lack the secondary elements of conventional benign fibrous histiocytoma and are positive for S100 protein and SOX10. Sclerosing perineurioma arises almost exclusively in the digits, an unusual site for fibrous histiocytomas, and is positive for EMA and GLUT-1. Occasional cases of interstitial granuloma annulare can superficially resemble benign fibrous histiocytoma. Evidence of collagen alterations and interstitial mucin helps in the distinction.

Aneurysmal fibrous histiocytoma may be confused with angiomatoid fibrous histiocytoma, though this is largely due to similarity in nomenclature, rather than any shared histopathologic features. Angiomatoid fibrous histiocytoma has a fibrous pseudocapsule with a peripheral lymphoid cuff, features not seen in aneurysmal fibrous histiocytoma. Angiomatoid fibrous histiocytoma is discussed in more detail in the next chapter.

Lipidized forms of benign fibrous histiocytoma should be distinguished from xanthogranuloma and xanthoma. The latter two lesions are more uniformly composed of histiocytes and lack overlying epidermal change and collagen trapping. Xanthogranuloma often has admixed eosinophils, which are not typically present in benign fibrous histiocytoma.

Atypical fibrous histiocytoma needs to be distinguished from atypical fibroxanthoma/pleomorphic dermal sarcoma, undifferentiated pleomorphic sarcoma, and pleomorphic fibroma. The tumors comprising the spectrum of atypical fibroxanthoma/pleomorphic dermal sarcoma can largely be excluded on clinical grounds, as the vast majority arise in sun-damaged skin of the head and neck. Undifferentiated pleomorphic sarcoma is larger and more deeply seated, has an infiltrative growth pattern and a more diffuse atypia, and is more mitotically active. Pleomorphic fibroma discussed above is often polypoid, consists of scattered pleomorphic cells without a distinctive growth pattern, is positive for CD34, and shows loss of RB1. None of these tumors have the background features of conventional fibrous histiocytoma present in all cases of atypical fibrous histiocytoma.

Multinucleate Cell Angiohistiocytoma

Clinical Features

Multinucleate cell angiohistiocytoma (MCAH) is a peculiar vascular and fibrohistiocytic lesion first described by Smith and Wilson Jones in 1985. While some regard it as an entity sui generis, others believe it to be a variant of fibrous histiocytoma (dermatofibroma) or angiofibroma (most notably fibrous papule of the face). As initially described, lesions are grouped, non-regressing asymptomatic, red-to-violaceous papules that develop over weeks to months on the face or acral sites of elderly women. Papules may coalesce or take on annular or linear configurations. Other variations from the initial clinical description include isolated papules arising at a variety of anatomic sites, coexisting epidermal proliferations or atrophy, fibrosis, and extensive angiomatous changes; a case with generalized distribution has also been reported. The clinical differential

diagnosis includes lichen planus, cutaneous lymphoid hyperplasia, Kaposi sarcoma, acroangiodermatitis (pseudo-Kaposi sarcoma), insect bites, granuloma annulare, and sarcoidosis. MCAH is a benign lesion with an indolent, but sometimes progressive, course. Spontaneous resolution has been reported, which some argue is supportive of a reactive rather than neoplastic process. Treatment is not necessary, but excision, cryotherapy, and lasers may be used to eradicate pruritic or cosmetically unacceptable lesions.

Pathologic Features

By histology MCAH are characterized by bizarre multinucleated cells with scalloped, angulated cytoplasm seen in association with a proliferation of dilated capillary dermal vessels, scattered lymphohistiocytic infiltrate, dense collagen in the upper dermis, and an increased number of interstitial mononuclear cells (Fig. 4.21a and b). Varying amounts of background fibrosis, epidermal hyperplasia, and mast cells may also be seen. By immunohistochemistry, mononuclear cells are positive for vimentin, FXIIIa, CD68, and lysozyme, but negative for S100 protein and CD1a. Multinucleated cells are positive for vimentin, and variably so for CD68, but negative for other monocyte/macrophage markers. Estrogen receptor (ER) positivity has been reported in interstitial and perivascular spindle cells and occasionally multinucleated cells. The etiology and pathogenesis of MCAH are largely unknown. The female predominance and ER positivity suggests the possibility of a hormonal

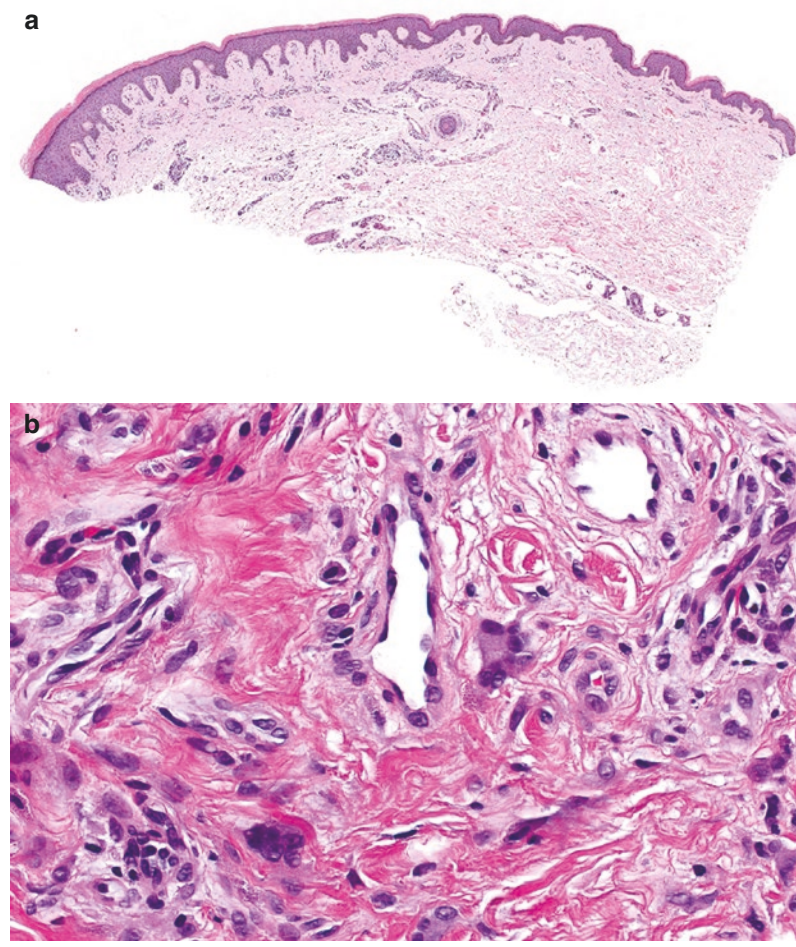


Fig. 4.21 Multinucleate cell angiohistiocytoma. (**a**) Dilated capillary dermal vessels. (**b**) Bizarre multinucleated cells with scalloped, angulated cytoplasm near dilated vessels

Table 4.21 Key pathologic features: multinucleated cell angiohistiocytoma

Bizarre multinucleated cells with scalloped, angulated cytoplasm
Proliferation of dilated capillary dermal vessels
Scattered lymphohistiocytic infiltrate
Dense collagen in the upper dermis
Increased interstitial mononuclear cells
Varying fibrosis, epidermal hyperplasia, and mast cells
Mononuclear cells positive for vimentin, Factor XIIIa, CD68, ER, and lysozyme and negative for S100 and CD1a
Multinucleated cells positive for vimentin, variably so for ER and CD68, but negative for other monocyte/macrophage markers

influence. IL-4 from mast cell degranulation has been postulated to play a role in the morphogenesis of the multinucleate cells. MCAH is a benign lesion with an indolent, but sometimes progressive, course (Table 4.21).

Differential Diagnosis

The histologic differential diagnosis of MCAH includes fibrous histiocytoma (dermatofibroma, particularly the atrophic vascular variant), angiofibroma (especially fibrous papule), Kaposi sarcoma and pseudo-Kaposi sarcoma (acroangiodermatitis), and microvenular hemangioma. Unlike dermatofibroma, MCAH typically arises in crops on the face and acral sites. Dermatofibromas more commonly have epidermal hyperplasia, collagen trapping, basal layer hyperpigmentation, a denser population of FXIIIa-positive dendrocytes, and more of a storiform growth pattern. Fibrous papule has an increased number of dilated capillaries and occasional multinucleated cells, but collagen bundles are perifollicular in distribution, or more vertically oriented and multinucleated cells are much fewer in number compared to MCAH. Kaposi sarcoma does not contain multinucleated cells and is HHV-8-positive. Pseudo-Kaposi sarcoma (acroangiodermatitis) tends to affect the lower extremities and has tortuous, thick-walled vessels and abundant hemosiderin deposition, unlike MCAH. Microvenular hemangioma consists of compressed venules lined by a prominent endothelium with surrounding pericyte layer and lacks multinucleated cells.

Epithelioid Fibrous Histiocytoma

Clinical Features

Epithelioid fibrous histiocytoma (EFH), also known as epithelioid histiocytoma, is now considered a distinct entity separate from the family of benign fibrous histiocytomas discussed above. Clinically, EFH usually presents on the extremities of young to middle-aged adults, as an erythematous, polypoid lesion. It is benign and cured by simple excision.

Pathologic Features

EFH is a well-circumscribed but unencapsulated tumor composed of uniform epithelioid to polygonal cells arranged in a sheetlike growth pattern (Fig. 4.22a). A dilated, sometimes branching, capillary vasculature is often seen at the periphery of the tumor. The individual tumor cells have enlarged, uniform nuclei with fine chromatin and a small nucleolus, and relatively abundant eosinophilic cytoplasm (Fig. 4.22b). Scattered mitotic figures may be seen, but cytologic atypia is minimal to absent. In contradistinction to dermatofibromas, collagen trapping is not a conspicuous feature. An epidermal collarette is often present in EFH. By immunohistochemistry, EFH is diffusely positive for FXIIIa. Recently, it has been documented that almost all EFH have rearrangements involving *ALK* and that close to 90% are positive for ALK by immunohistochemistry, which correlates with *ALK* gene rearrangement (Fig. 4.22c). EFH are often positive for EMA and are negative for cytokeratins and S100 protein (Table 4.22).

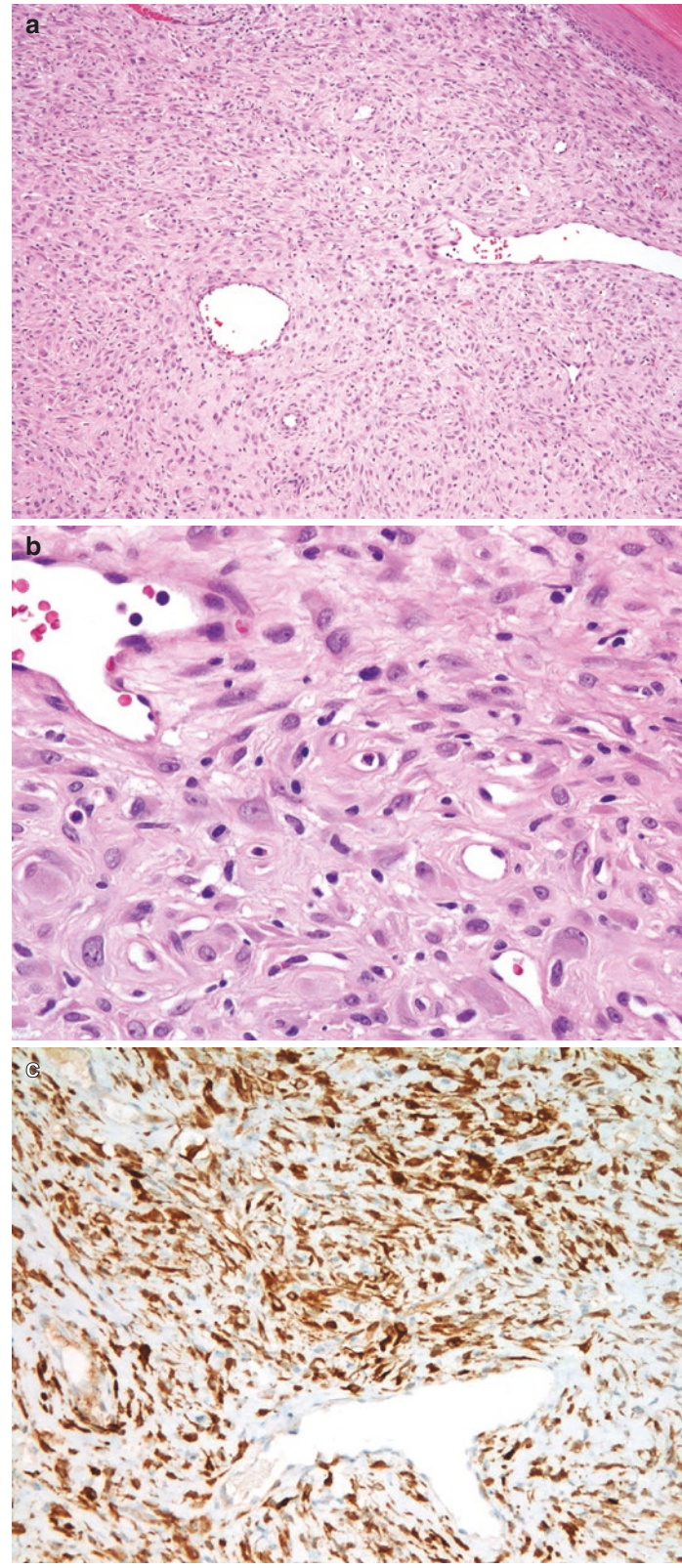


Fig. 4.22 Epithelioid fibrous histiocytoma. (**a**) Sheetlike growth of uniform epithelioid cells. Dilated vessels are seen at the periphery. (**b**) Individual tumor cells have enlarged, uniform nuclei with fine chromatin and a small nucleolus, and an abundant amount of eosinophilic cytoplasm. (**c**) ALK positivity in epithelioid fibrous histiocytoma

Table 4.22 Key pathologic features: epithelioid fibrous histiocytoma

Well-circumscribed dermal proliferation of uniform epithelioid to polygonal cells with abundant eosinophilic cytoplasm arranged in a sheetlike growth pattern
Epidermal collarette
Dilated capillary vasculature
Scattered mitotic figures but limited cytologic atypia
ALK rearrangements with close to 90% are positivity for ALK by IHC
Positive for FXIIIa and often EMA, negative for cytokeratins and S100

Differential Diagnosis

Perhaps the most difficult differential diagnosis is with cutaneous syncytial myoepithelioma (CSM). Both have similar cytomorphologic features. However, CSM is positive for EMA and typically variably positive for S100 protein, cytokeratins, and SOX10, but negative for ALK. CSM also demonstrates *EWSR1* rearrangement by FISH, which is not seen in EFH. Cellular neurothekeomas (CNTK) are more spindled and nested, lack a polypoid silhouette, and are positive for NKI-C3, PGP9.5, and CD10, unlike EFH. Neither CSM nor CNTK are immunoreactive for ALK by immunohistochemistry. Spitz nevi enter the differential diagnosis due to shared epithelioid cytomorphology, but are also immunoreactive for melanocytic markers, such as S100 protein, Melan-A, MiTF, and SOX10. Of note, a subset of Spitz nevi are also positive for ALK. Conventional DF may enter the differential, but are distinguished by the presence of secondary elements (Touton-type giant cells, hemosiderin, foam cells), peripheral collagen trapping, and lack of immunoreactivity for ALK and EMA.

Juvenile (Solitary) Xanthogranuloma

Clinical Features

Solitary (juvenile) xanthogranuloma (JXG) is a benign soft tissue tumor belonging to the broad group of non-Langerhans cell histiocytoses that occurs without gender predilection most frequently in children, including a significant portion of congenital lesions. JXG typically present as a solitary, slow-growing cutaneous papule or nodule of the head and neck, chest, abdomen, or extremities, although a subset of multifocal tumors in children (<5% of cases) will involve the eye, deep soft tissues, or visceral organs (i.e., liver, lung, etc.). JXG near the eye in children should prompt ophthalmologic referral to rule out eye and ocular adnexal involvement. Juvenile myelomonocytic leukemia (JMML), as well as germline mutations in *NF1* and *NF2*, has been reported in children with JXG. Tumors that present in children frequently grow and then spontaneously regress, leaving only hyperpigmented skin, while tumors that present in adulthood may persist as a mass lesion. Xanthogranuloma is a benign lesion, with infrequent local recurrence after surgical excision. Extraordinarily rare cases of death have been reported in patients with multifocal, systemic disease. Symptomatic patients with multisystem disease can successfully be treated with LCH-based regimens that include both corticosteroids and vinca alkaloids.

Pathologic Features

JXG are unencapsulated, but circumscribed, hypercellular tumors comprised predominantly of bland-appearing histiocytes with abundant pale cytoplasm and enlarged, slightly irregular vesicular nuclei with conspicuous nucleoli. Tumor cells are arranged in diffuse nodular sheets within the dermis and frequently closely abut the overlying flattened epidermis (Fig. 4.23a). In most cases, varying numbers of giant cells, including Touton and osteoclast-type giant cells, are distributed evenly throughout the tumor, and a conspicuous mixed acute and chronic inflammatory infiltrate with lymphocytes, eosinophils, and plasma cells is present (Fig. 4.23b). It should be noted that early tumors and visceral forms may lack Touton-type giant cells and an inflammatory infiltrate. In some tumors, there is prominent intracytoplasmic lipid accumulation, and regressed tumors may show

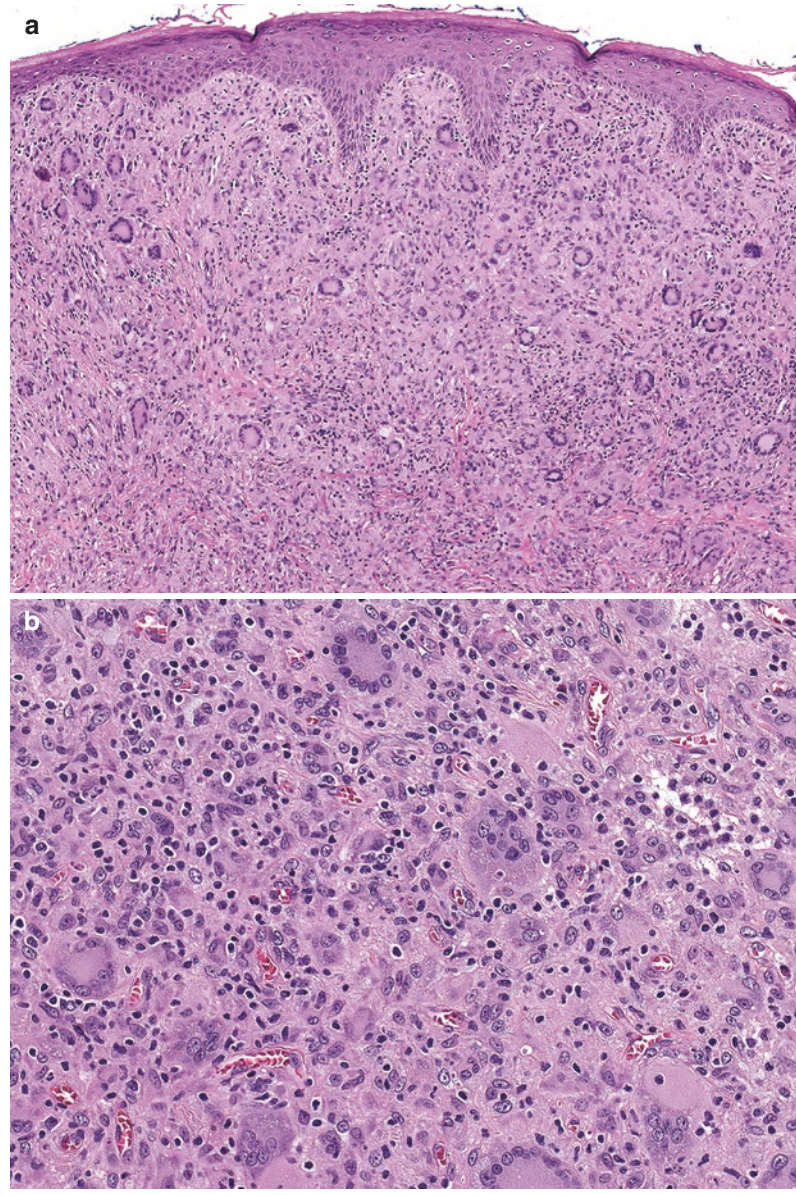


Fig. 4.23 Juvenile (solitary) xanthogranuloma. (**a**) The tumor cells are arranged in diffuse nodular sheets within the dermis abutting the epidermis. (**b**) Touton- and osteoclast-type giant cells are distributed evenly with admixed inflammatory cells

fibrosis with a storiform growth pattern. Tumor cells express CD68, CD163, and FXIIIa but are negative for S100 protein and CD1a expression.

Molecular studies have provided evidence of clonality in juvenile xanthogranuloma, in support of a neoplastic process. Recently, mutations involving *NRAS*, *KRAS*, *ARAF*, or *MAP2K1* were found in 7 out of 12 systemic juvenile xanthogranuloma cases, suggesting a role for MAPK signaling in JXG. Two cases of mixed Langerhans cell histiocytosis/juvenile xanthogranuloma have been reported to have V600E mutations, and a *RNF11-BRAF* fusion was identified in one case of systemic juvenile xanthogranuloma. A *PIK3CD* mutation in serial biopsies from a single patient suggests that the PI3K pathway may also be involved in juvenile xanthogranuloma progression. Finally, copy number alterations or copy neutral loss of heterozygosity including trisomy 5 and 17 and loss of heterozygosity in 5q have been reported in two lesions from a case of diffuse JXG. The same study found only two

Table 4.23 Key pathologic features: solitary (juvenile) xanthogranuloma

Circumscribed hypercellular tumor composed of bland histiocytes with abundant pale cytoplasm
Variable numbers of giant cells, particularly of the Touton-type
Mixed acute and chronic inflammation with lymphocytes, eosinophils, and plasma cells
Early and visceral lesions may lack Touton-type giant cells and inflammation
Older lesions may show more spindle cells, a storiform growth pattern, and fibrosis
Positive for CD68, CD163, and Factor XIIIa, negative for S100 and CD1a

cases of solitary JXG with molecular abnormalities, one showing gains on 1q and 11q and the other loss in 3p (Table 4.23).

Differential Diagnosis

The differential diagnosis for solitary (juvenile) xanthogranuloma includes xanthoma, benign fibrous histiocytoma, and solitary reticulohistiocytoma. Although some xanthoma subtypes may show multinucleated osteoclast-type giant cells, Touton-type giant cells are typically absent. Benign fibrous histiocytomas may have Touton-type giant cells, but typically are more polymorphous and have collagen trapping and frequently epidermal hyperplasia. Solitary reticulohistiocytoma has ground-glass histiocytes, lacks Touton giant cells, and is negative for Factor XIIIa expression.

Solitary Reticulohistiocytoma/ Multicentric Reticulohistiocytosis

Clinical Features

Solitary reticulohistiocytoma is a rare benign soft tissue tumor with slight male predominance that typically occurs in younger adults. Tumors usually present as a solitary slowly enlarging cutaneous soft tissue mass in the chest, abdomen, extremities, or head and neck and do not recur after surgical excision.

Multicentric reticulohistiocytosis is a multifocal counterpart to solitary reticulohistiocytoma. It usually presents in middle-aged adults with a slight female predominance. Lesions present as multiple slowly enlarging soft tissue masses in the skin, mucosa, soft tissue, and/or joints. A subset of cases may be associated with a rheumatologic disorder or underlying malignancy, such as carcinoma of the breast, lung, colon, ovary, or cervix, as well as sarcoma and lymphoma. Multicentric reticulohistiocytosis often shows a variable clinical course, with periods of relative improvement and worsening of disease. Some patients develop significant arthritis with deforming arthropathy. In patients with a malignancy or rheumatologic disorder, treatment of the underlying condition may improve the clinical symptoms associated with multicentric reticulohistiocytosis.

Pathologic Features

Microscopically, tumors are circumscribed, unencapsulated tumors comprised predominantly of large epithelioid histiocytes with abundant pale to eosinophilic cytoplasm, enlarged and irregular vesicular nuclei, prominent nucleoli, and frequent multinucleation (Fig. 4.24). Tumor cells are arranged in diffuse nodular sheets within the dermis, with prominent admixed collagen bundles; a conspicuous chronic inflammatory infiltrate is often present as well. Although focally increased cytologic atypia and mitotic activity may be noted, necrosis is not identified. Tumor cells express CD68 and CD163, but are negative for Factor XIIIa, S100, and CD1a expression. The pathologic findings in multicentric reticulohistiocytosis are identical to those of the solitary form (Table 4.24).

Differential Diagnosis

The differential diagnosis of solitary reticulohistiocytoma includes Langerhans cell histiocytosis, Rosai-Dorfman disease, epithelioid fibrous histiocytoma, and benign fibrous histiocytoma. In

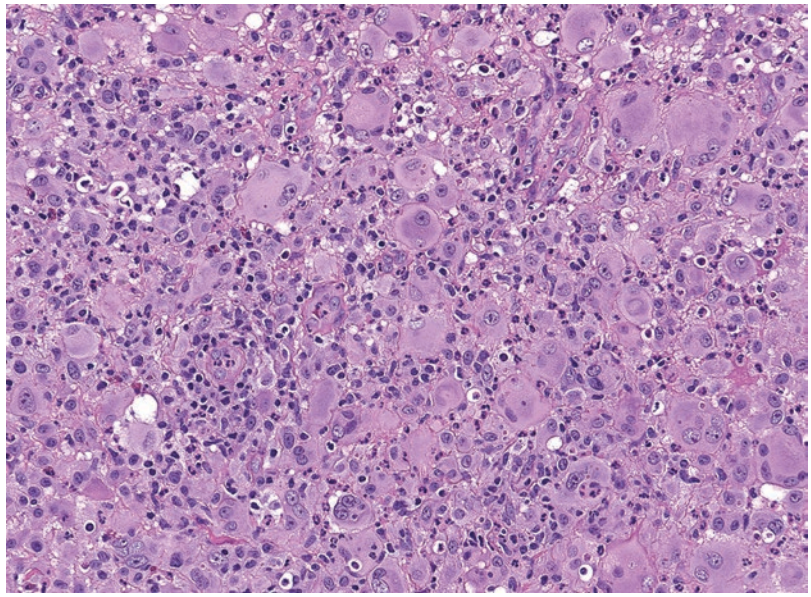


Fig. 4.24 Solitary reticulohistiocytoma/multicentric reticulohistiocytosis. Large epithelioid histiocytes with abundant pale to eosinophilic cytoplasm, enlarged and irregular vesicular nuclei, prominent nucleoli, and frequent multinucleation. Note the associated inflammatory infiltrate

Table 4.24 Key pathologic features: solitary reticulohistiocytoma/multicentric reticulohistiocytosis

Circumscribed but unencapsulated proliferation of deeply eosinophilic (ground-glass) epithelioid cells among scattered inflammation
Multinucleation and spindling of cells common
Only mild atypia and occasional mitoses
Positive for CD68 and CD163, variable immunoreactivity for lysozyme, negative for S100 protein

contrast to reticulohistiocytoma, Langerhans cell histiocytosis and Rosai-Dorfman disease both express S100 protein and, in the case of Langerhans cell histiocytosis, CD1a. Epithelioid fibrous histiocytoma is positive for ALK and often has a more conspicuous capillary vasculature. Benign fibrous histiocytoma is more polymorphous and has peripheral collagen trapping.

The differential diagnosis for multicentric reticulohistiocytosis is similar to that discussed above for solitary reticulohistiocytoma; however, given its unique clinical associations (including the possibility of concurrent malignancy or rheumatologic disease) and variable, but often progressive clinical course, it is important to distinguish multicentric reticulohistiocytosis from solitary reticulohistiocytoma on clinical findings.

Xanthomas

Clinical Features

Xanthoma is a benign soft tissue lesion that occurs due to accumulation of excess serum lipids, most frequently in patients with hyperlipoproteinemias. These lesions typically present as a slowly growing cutaneous soft tissue mass, but may occur in tendons, synovium, deep soft tissue, and/or bone. There are five types of xanthoma: eruptive, tuberous, plane, xanthelasma, and tendinous. Eruptive xanthomas typically occur in patients with types I, III, or V hyperlipoproteinemia, are small and multiple, and show predilection for the buttocks. Eruptive xanthomas can also occur as a reaction to tattoos. Tuberous xanthomas usually arise in patients with types IIa or III hyperlipoproteinemia, are large with plaque-like growth, and demonstrate predilection for the buttocks,

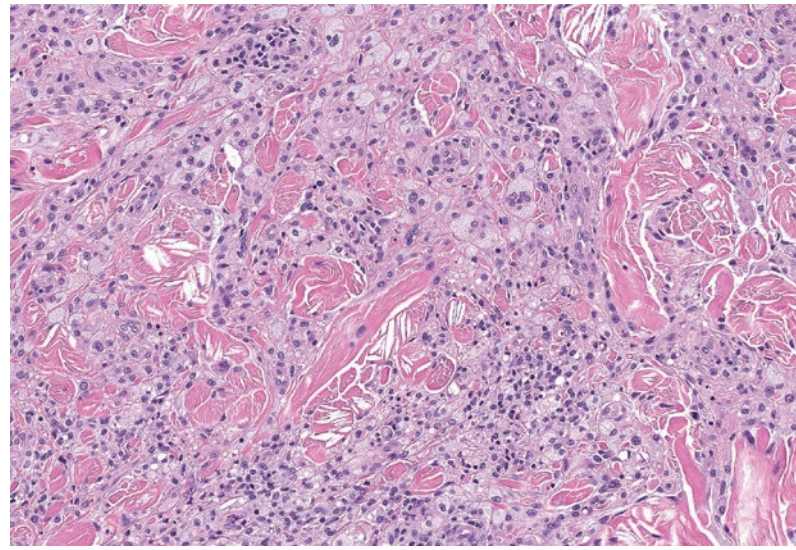


Fig. 4.25 Xanthoma. Relatively hypercellular lesion composed predominantly of lipid-laden ("foamy") histiocytes with moderate pale to amphophilic cytoplasm, small pyknotic nuclei, and inconspicuous nucleoli, arranged in diffuse nodular sheets within the dermis

knees, elbows, and fingers. Plane xanthomas are typically found in the palmar creases of patients with primary biliary cirrhosis III, but may also be present in normolipemic patients with an underlying hematolymphoid malignancy. Xanthelasmas arise on the eyelids of patients with types IIa or III hyperlipoproteinemia. Finally, tendinous xanthomas occur in patients with type IIa hyperlipoproteinemia or cerebrotendinous xanthomatosis. Because xanthomas represent a reactive accumulation of lipid-laden histiocytes often due to excess serum lipids, they may regress with systemic medical therapy; surgical excision is generally not necessary.

Pathologic Features

Grossly, xanthomas are unencapsulated, but well-circumscribed skin and/or soft tissue lesions. Microscopically, xanthomas are relatively hypercellular and composed predominantly of lipid-laden ("foamy") histiocytes with moderate pale to amphophilic cytoplasm, small pyknotic nuclei, and inconspicuous nucleoli, arranged in diffuse nodular sheets within the dermis (Fig. 4.25). In addition to foamy histiocytes, eruptive xanthomas show numerous admixed non-foamy histiocytes and chronic inflammatory cells, while tuberous and tendinous xanthomas frequently contain cholesterol clefts with multinucleated giant cells and fibrosis (Table 4.25).

Table 4.25 Key pathologic features: xanthoma

Foamy macrophages admixed with inflammatory cells
Cholesterol clefts flanked by multinucleated giant cells
Varying fibrosis, most conspicuous in long-standing lesions
Eruptive xanthoma has larger proportion of non-foamy macrophages
Sheets of xanthoma cells and less fibrosis in plane xanthoma and xanthelasma

Differential Diagnosis

While the diagnosis of xanthoma is often straightforward, some xanthoma subtypes may show morphologic overlap with other benign or intermediate malignant soft tissue tumors, including benign fibrous histiocytoma, solitary (juvenile) xanthogranuloma, tenosynovial giant cell tumor, and giant cell tumor of soft tissue. Peripheral collagen-trapping and the presence of non-foamy histiocytes favor a diagnosis of benign fibrous histiocytoma, while the presence of Touton-type multinucleated giant cells is consistent with solitary (juvenile) xanthogranuloma. Finally, tenosynovial giant cell tumor and giant cell tumor of soft tissue both show a prominent population of

epithelioid histiocyte-like mononuclear cells, which are not typically seen in xanthomas.

Tenosynovial Giant Cell Tumor

Clinical Features

Tenosynovial giant cell tumor (TSGCT) is a benign soft tissue tumor with slight female predominance that typically occurs in middle-aged patients. Tumors usually present as a slowly enlarging soft tissue mass along tendons of the hands and feet or associated with large joints, including the knee, ankle, and wrist. There are two types of tenosynovial giant cell tumor: localized and diffuse. The localized type (also known as giant cell tumor of tendon sheath) most commonly involves the digits of the hands and has a relatively low, but significant risk of local recurrence after surgical excision. In contrast to the localized type, the diffuse type (also known as extra-articular pigmented villonodular synovitis) is relatively uncommon, occurs in a younger age group, and is characterized by extra-articular soft tissue involvement with predilection for the knee; diffuse type tumors show a significant local recurrence rate after surgical excision and may be associated with malignant transformation and subsequent metastasis. Radiotherapy alone or in combination with surgical excision may decrease the likelihood of recurrence of diffuse-type tenosynovial giant cell tumor. Clinical trials of agents such as imatinib mesylate that target the CSF1 receptor are ongoing.

Pathologic Features

All tenosynovial giant cell tumors show common morphologic features; however, there are characteristic gross and microscopic differences between the localized and diffuse types. Grossly, most localized type tenosynovial giant cell tumors are small, encapsulated, circumscribed solid masses with firm tan cut surfaces. In contrast, diffuse type tumors tend to be larger, unencapsulated, and poorly circumscribed; in addition, they may have a conspicuous pigmented "rust-brown" appearance and typically show prominent villonodular growth (for obvious reasons, such tumors have also been called "pigmented villonodular synovitis"). Microscopically, both types of tenosynovial giant cell tumor are typically hypercellular and composed of varying amounts of three cell types: epithelioid mononuclear cells, multinucleated giant cells, and foamy histiocytes (Fig. 4.26a). It should be noted that occasional cases have very few multinucleated giant cells (giant cell-poor TSGCT). In addition, the diffuse type of TSGCT usually shows conspicuous villonodular architecture and intratumoral hemosiderin accumulation/deposition (Fig. 4.26b). Mitoses up to 3/10 high-power fields may be seen in greater than 10% of cases, but this does not portend a more aggressive clinical course. Rare malignant diffuse-type TSGCTs (malignant pigmented villonodular synovitis) show significant cytologic atypia, mitotic activity, and foci of necrosis (Fig. 4.26c). The epithelioid mononuclear cells of TSGCT express clusterin and are often positive for MiTF (a significant pitfall), but are negative for CD163, though entrapped histiocytes are CD163-positive. TSGCT also can contain desmin-positive dendritic cells, which may be mistaken for evidence of rhabdomyosarcoma. Tenosynovial giant cell tumors harbor characteristic *CSF1* gene fusions, most commonly a *COL6A3-CSF1* gene fusion resulting from t(1;2) genomic rearrangements (Table 4.26).

Differential Diagnosis

The differential diagnosis for TSGCT includes fibroma of tendon sheath, xanthoma, benign fibrous histiocytoma, and giant cell tumor of soft tissue. Although they share some clinical features, fibroma of tendon sheath does not show the characteristic foamy histiocytes or multinucleated osteoclast-type giant cells of tenosynovial giant cell tumor. Similarly, the presence of a distinct population of epithelioid histiocyte-like mononuclear cells argues against xanthoma and benign fibrous histiocytoma. Finally, while

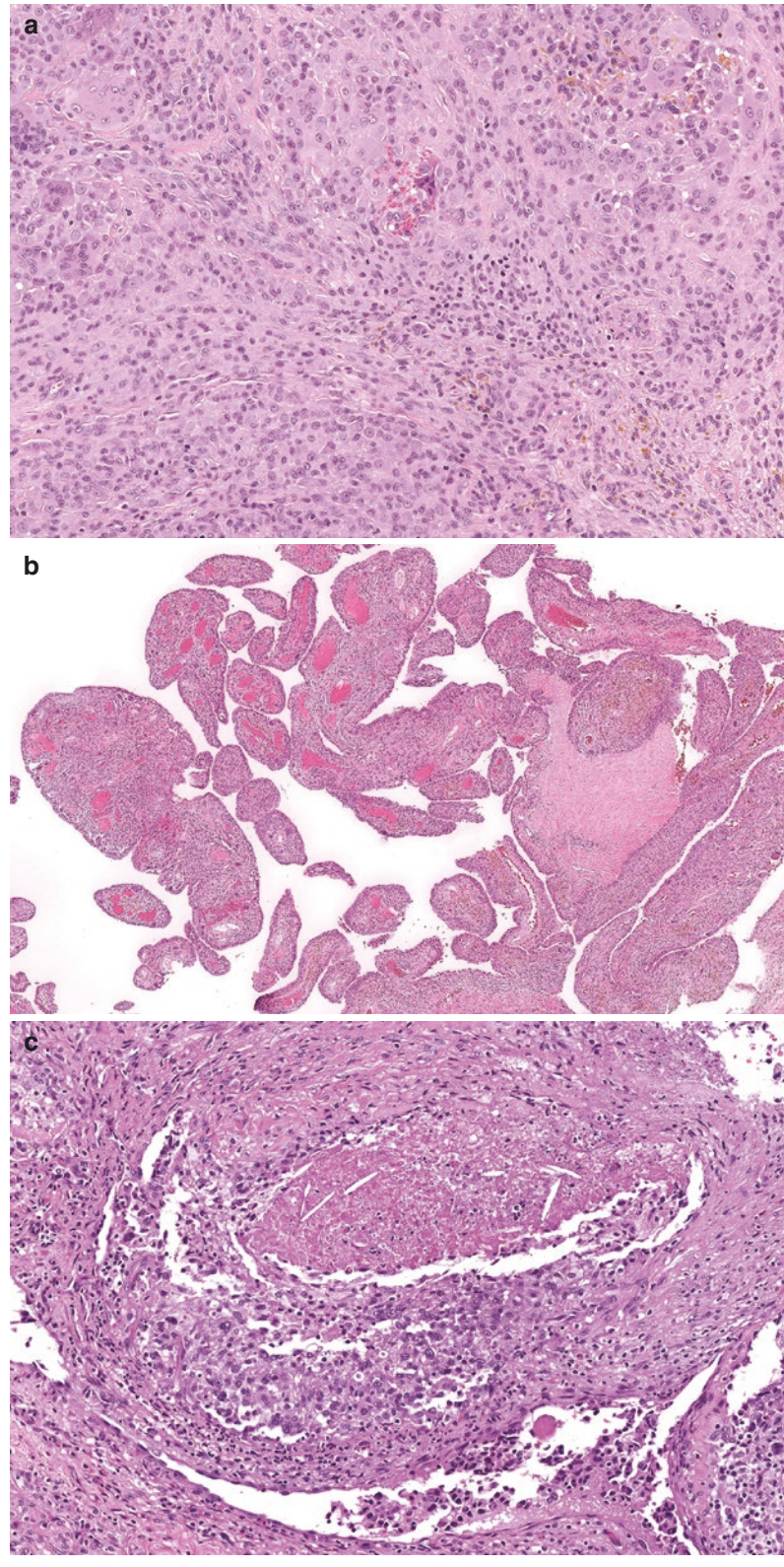


Fig. 4.26 Tenosynovial giant cell tumor. (**a**) Hypercellular lesion comprised of varying amounts of three cell types: epithelioid mononuclear cells, multinucleated giant cells, and foamy histiocytes. (**b**) Diffuse type of tenosynovial giant cell tumors usually shows conspicuous villonodular architecture and intratumoral hemosiderin accumulation/deposition. (**c**) Malignant tenosynovial giants cell tumor with necrosis

Table 4.26 Key pathologic features: tenosynovial giant cell tumor

Tenosynovial giant cell tumor – localized type
Small, well-circumscribed lobulated mass often associated with tendon sheath
Moderately cellular tumor composed of sheets of polygonal-to-round cells
Hypocellular collagenized zones
Scattered multinucleated giant cells
Varying proportions of foam cells, hemosiderin, giant cells, mononuclear cells, and collagen
Rare cartilaginous and osseous metaplasia
Tenosynovial giant cell tumor – diffuse type
Poorly circumscribed, extensively destructive mass associated with large joints
Pronounced cellularity with expansive sheets of round-to-polygonal cells punctuated by pseudoglandular spaces
Less numerous giant cells
Other features similar to localized type tenosynovial giant cell tumor
Malignant diffuse-type tenosynovial giant cell tumor (malignant pigmented villonodular synovitis)
As per diffuse-type tenosynovial giant cell tumor with the addition of significant cytologic atypia and mitotic activity and foci of necrosis

TSGCT and giant cell tumor of soft tissue show significant morphologic overlap, clinical features (including anatomic site) should assist in this differential diagnosis; in addition, in contrast to tenosynovial giant cell tumor, giant cell tumor of soft tissue often shows a multinodular growth pattern with prominent intervening fibrous septa.

Superficial Acral Fibromyxoma (Digital Fibromyxoma) and Cellular Digital Fibroma

Clinical Features

Superficial acral fibromyxoma (SAF) is a benign soft tissue tumor with a male predominance that typically occurs in middle-aged adults. Tumors nearly always present as a slowly growing soft tissue mass on the finger or toe, most commonly associated with the nail bed. Cellular digital fibroma (CDF) likely represents a variant of SAF. It tends to be smaller, but otherwise has the same clinical presentation. SAF may also be related to the acral fibrokeratomas, which some consider a subset of acral angiofibromata (see above). Superficial acral fibromyxoma is benign, but may recur locally (~20%), likely the result of the difficulty of achieving negative margins in acral locations. Conservative, but complete excision is recommended.

Pathologic Features

SAF is unencapsulated and relatively circumscribed and almost always arises adjacent to the nail bed (Fig. 4.27a). It is somewhat hypocellular and comprised predominantly of small bland-appearing spindle cells with scant eosinophilic cytoplasm and hyperchromatic tapered nuclei with inconspicuous nucleoli. Tumor cells are evenly distributed within a variably fibrous and myxoid stroma containing frequent admixed small vessels (Fig. 4.27b). Multinucleated stromal cells and associated mast cells may be present. Cytologic atypia and mitotic activity is minimal, and necrosis is not identified. CDF is more cellular and composed of shorter fascicles of bland spindled cells (Fig. 4.27c). SAF and CDF consistently express CD34. SAF may show some immunoreactivity for EMA, SMA, CD10, and nestin and shows frequent loss of RB1 expression. The tumor cells are negative for desmin, S100 protein, MUC4, STAT6, GFAP, and pan-cytokeratin (Table 4.27).

Differential Diagnosis

The differential diagnosis for SAF includes cutaneous myxoma, neurofibroma, dermatofibrosarcoma protuberans, sclerosing perineurioma, and low-grade fibromyxoid sarcoma. SAF is a more cellular lesion than cutaneous myxoma and the stroma contains more collagen. In contrast to neurofibroma, the tumor cells of SAF are not comma-shaped, and the vasculature is more conspicuous. SAF is also negative for S100 protein. Dermatofibrosarcoma protuberans is more cellular than SAF. CDF is more likely to be confused with dermatofibrosarcoma protuberans in that it

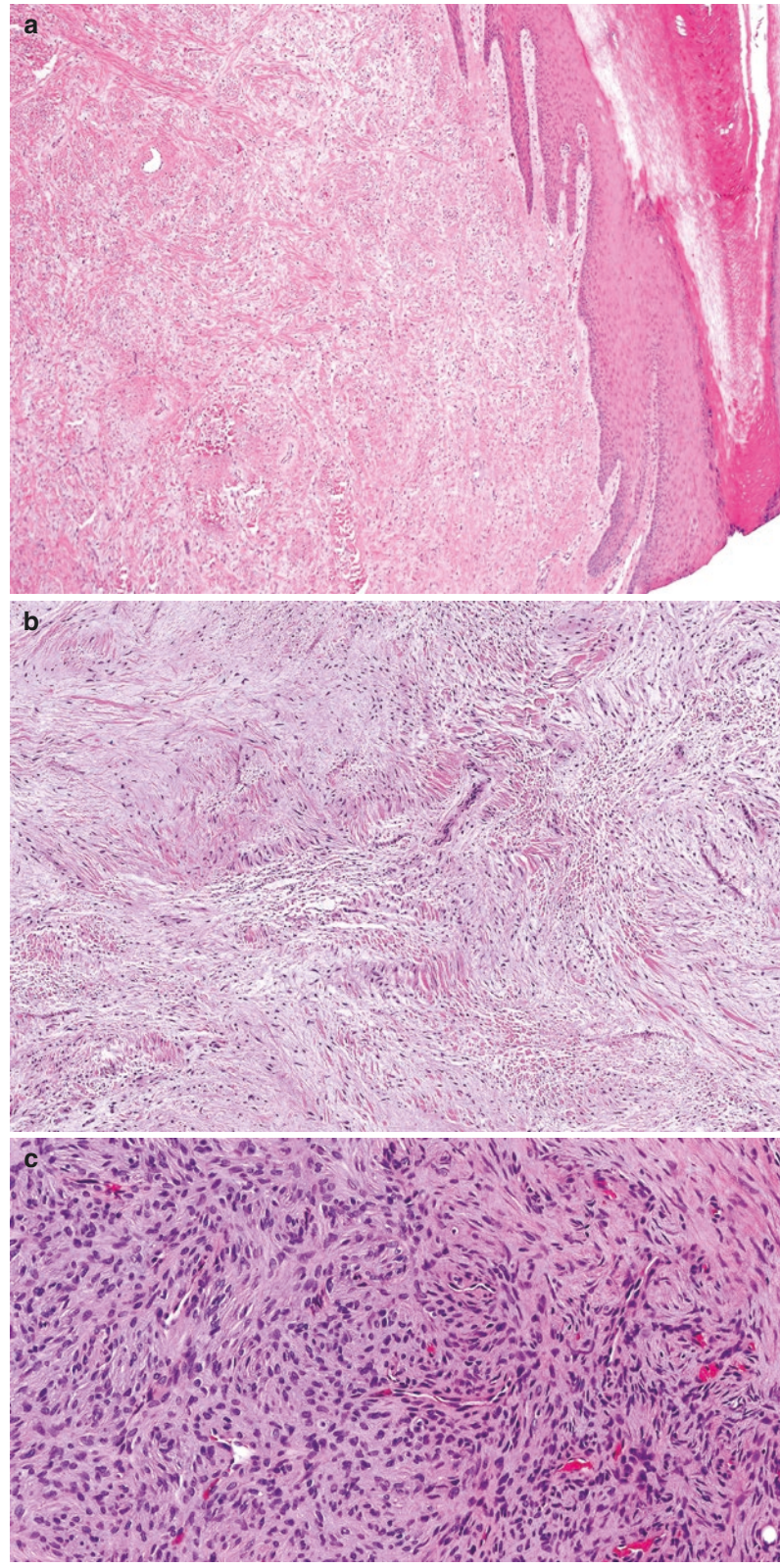


Fig. 4.27 Superficial acral fibromyxoma (digital fibromyxoma) and cellular digital fibroma. (**a**) Superficial acral fibromyxoma is an unencapsulated but circumscribed hypocellular lesion that nearly always arises adjacent to the nail bed. (**b**) The bland spindle cells are set within a fibrous and myxoid stroma containing small vessels. (**c**) Cellular digital fibroma is more cellular with short fascicles of bland spindled cells

Table 4.27 Key pathologic features: superficial acral fibromyxoma (digital fibromyxoma) and cellular digital fibroma

Hypocellular proliferation of bland spindle cells
Variable fibrous-to-myxoid stroma containing small vessels
Multinucleated stromal and mast cells may be present
CDF is likely a more cellular variant of SAFM composed of shorter fascicles of bland spindled cells
SAF and CDF consistently express CD34. SAF shows variable staining with EMA, SMA, CD10, and nestin and has frequent loss of RB1 expression. Both are negative for desmin, S100, MUC4, STAT6, GFAP, and pan-cytokeratin

is more cellular than SAF, but it can be distinguished by its circumscription and lack of a storiform growth pattern. Dermatofibrosarcoma protuberans demonstrates a *COL1A1-PDGFRB* fusion, while SAF and CDF do not. Sclerosing perineurioma has a cord-like growth pattern and lacks myxoid stroma and a conspicuous vasculature. Low-grade fibromyxoid sarcoma typically has abrupt transitions from cellular fibrous to hypocellular myxoid zones and is positive for MUC4.

Cutaneous Myxoma/Superficial Angiomyxoma

Clinical Features

Cutaneous myxomas are benign paucicellular multilobular, papulonodular, or polypoid lesions commonly occurring in adults (median age of 45.5 years). Lesions arise on the trunk, head and neck, or lower limbs most often; there is no sexual predisposition. Multiple lesions are associated with Carney complex, but multiple lesions have been described in the absence of this syndrome. Cutaneous myxomas are benign, but may recur in up to 38% of cases when incompletely excised.

Pathologic Features

Lesions are typically poorly circumscribed, but a multilobular silhouette is often present (Fig. 4.28a). Lobules are composed of an abundant myxoid stroma containing stellate to bipolar fibroblastic cells in association with mucin pools, a sparse mixed inflammatory infiltrate characteristically containing scattered neutrophils, and numerous small blood vessels. Lesions with an extensive vasculature are often designated as superficial angiomyxomas (Fig. 4.28b). There is little to no cytologic atypia or mitotic activity encountered. Isolated epithelial elements including epidermal inclusion cysts, strands of squamous or basaloid epithelium, and adnexal induction may be seen, particularly in the setting of Carney complex (Fig. 4.28c).

By immunohistochemistry constituent cells may be variably positive for SMA, typically in a tram-track myofibroblastic pattern of immunoreactivity. Cytokeratins, S100 protein, FXIIIa, desmin, and CD68 stains are negative. Some studies have found focal CD34 positivity. Patients presenting with multiple lesions in the setting of Carney complex have a mutation in the *PRKAR1A* gene, which encodes one of the four subunits of protein kinase A (Table 4.28).

Differential Diagnosis

Cutaneous myxomas can be confused with other myxoid lesions, which may arise in the skin and superficial soft tissues including myxofibrosarcoma, aggressive angiomyxoma, dermal nerve sheath myxoma, trichodiscoma/fibrofolliculoma, and focal cutaneous mucinoses. Myxofibrosarcoma is typically a larger lesion originating in the deeper soft tissues and secondarily extending into the skin with significant cytologic atypia and pleomorphism, and a characteristic arcuate vasculature with prominent tumor cell condensation. Imaging studies will also reveal a larger deep-seated mass. Cutaneous angiomyxomas involving the genital region should be distinguished from aggressive angiomyxoma, which is typically a more deeply seated, large mass within pelvic soft tissues that is extensively infiltrative and has a characteristic vasculature composed of small capillaries and thick-walled vessels with distinct perivascular

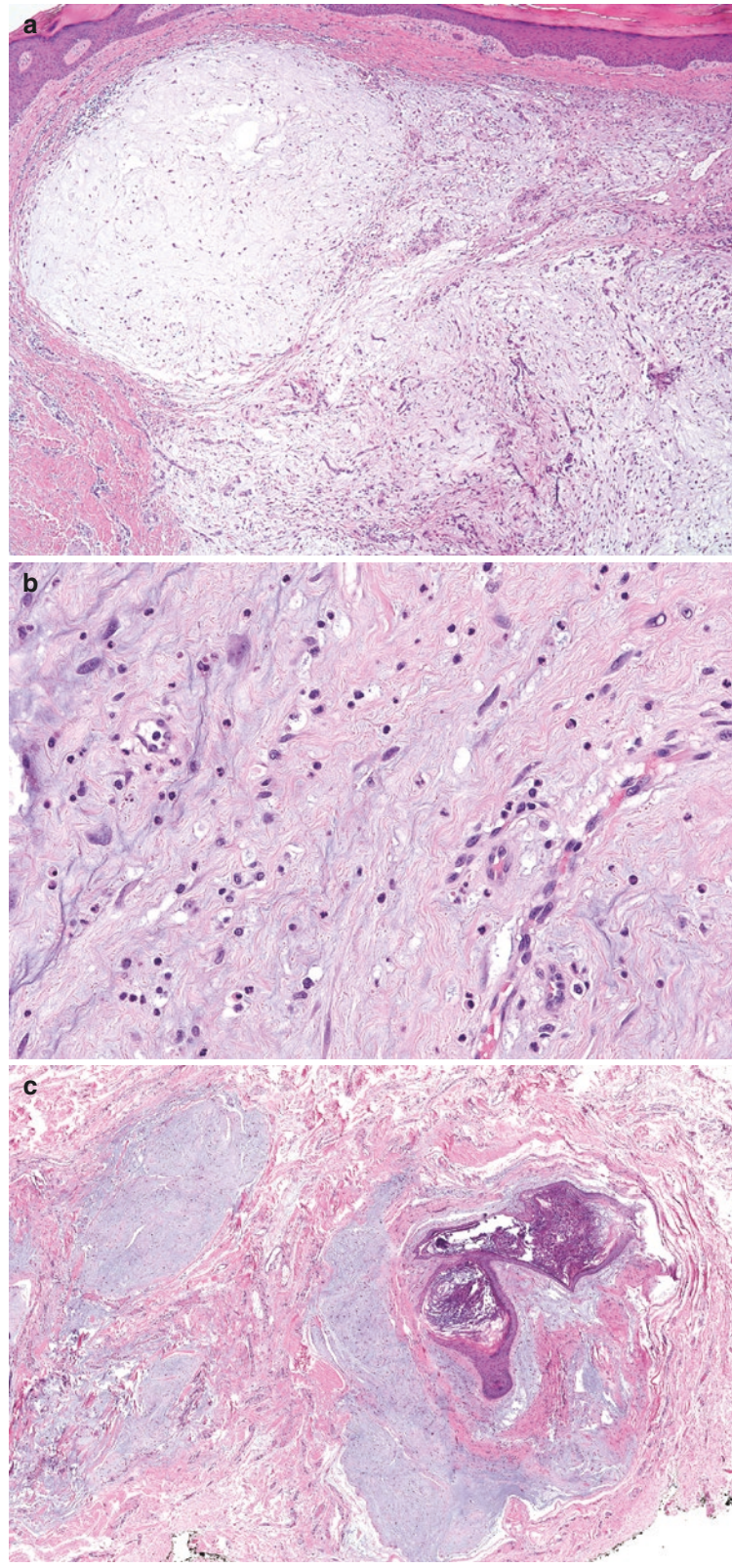


Fig. 4.28 Cutaneous myxoma/superficial angiomyxoma. (**a**) Cutaneous myxoma. A myxoid dermal tumor with a multilobular architecture. (**b**) Superficial angiomyxoma with prominent vessels and neutrophils. (**c**) Isolated epithelial elements, including epidermal inclusion cysts, may be seen

Table 4.28 Key pathologic features: cutaneous myxoma/superficial angiomyxoma

Poorly circumscribed myxoid nodules with lobular silhouette
Stellate to bipolar fibroblastic cells and muciphages
Sparse mixed inflammatory infiltrate characteristically containing neutrophils
Varying cellularity
Numerous small blood vessels (when prominent designated as superficial or cutaneous angiomyxoma)
Positive for SMA (tram-track myofibroblastic pattern), variable CD34 immunoreactivity
Negative for S100 protein, FXIIIa, and desmin

hyalinization. Dermal nerve sheath myxoma typically arises in the extremities, particularly the fingers, and has more spindled to epithelioid Schwann cells present in nests, cords and syncytial aggregates; these cells are positive for S100 protein, GFAP, neuron-specific enolase, p75, and CD57, all of which are negative in cutaneous myxomas. Myxoid variants of trichodiscoma/fibrofolliculoma may also enter the differential diagnosis of cutaneous myxoma. Trichodiscoma/fibrofolliculoma is predominantly a fibrous tumor associated with hair follicles. These lesions likely arise from perifollicular mesenchymal spindle cells and present in the head and neck region.

Cellular Neurothekeoma

Clinical Features

Cellular neurothekeoma (CNTK) is a benign soft tissue tumor with a female predominance that typically occurs in younger adults. Tumors usually present as a slowly enlarging cutaneous soft tissue mass of the head and neck or extremities and only rarely recur after surgical excision.

Pathologic Features

Cellular neurothekeoma is a circumscribed tumor arising in the dermis. It is typically composed of discrete nests or fascicles of epithelioid to spindled cells often delineated by fibrous septa (Fig. 4.29a and b). The tumor cells have oval nuclei with fine chromatin, small nucleoli, and relatively abundant eosinophilic cytoplasm. In some cases, hemorrhage and osteoclast-type giant cells are present in tumor nests. Focal nuclear atypia is relatively common and is sometimes prominent (atypical cellular neurothekeoma) (Fig. 4.29c). Constituent spindle cells are embedded in a collagenous stroma, but focal myxoid change is relatively common. Predominately myxoid variants (Fig. 4.29d) have been described as well as variants with prominent hyalinized stroma (desmoplastic cellular neurothekeoma) (Fig. 4.29e). Tumors may also be more cellular with solid sheets and fascicles of tumor cells. Perineural invasion and lymphovascular invasion have also been described in atypical cellular neurothekeoma, but none of these features seem to impact clinical behavior. Tumor cells express NKI-C3, CD10, and PGP9.5, though none of these markers are terribly specific and thus need to be interpreted in light of the histologic features. Variable expression of MiTF (60–80%) and SMA is seen (10–50%). The tumor cells are negative for SOX10, S100 protein, CD34, desmin, and pan-cytokeratin expression.

Originally considered a nerve sheath tumor due to morphologic similarity to dermal nerve sheath myxoma (myxoid neurothekeoma), cellular neurothekeoma is now considered a fibrohistiocytic tumor. No definitive ultrastructural or immunophenotypic evidence of nerve sheath differentiation has been reported. Genetic analysis of cellular neurothekeoma has demonstrated overlap with benign fibrous histiocytomas (Table 4.29).

Differential Diagnosis

The differential diagnosis for neurothekeoma includes dermal nerve sheath myxoma, plexiform fibrohistiocytic tumor, benign fibrous histiocytoma, and melanocytic tumors. Dermal nerve sheath myxoma has distinct fibrous septations,

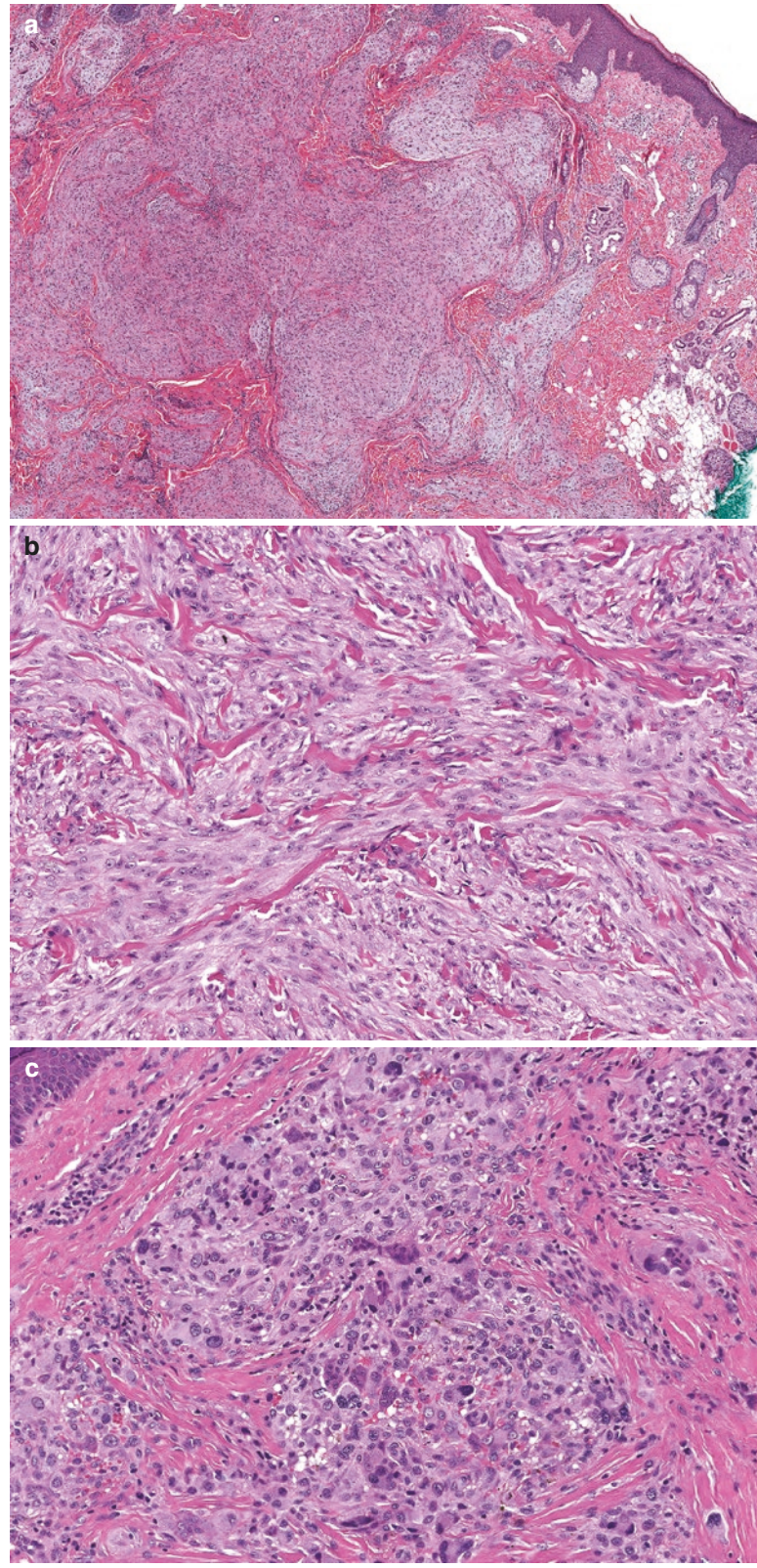


Fig. 4.29 Cellular neurothekeoma. (**a**) Circumscribed tumor in dermis comprised of nests of bland spindle cells delineated by fibrous septa. (**b**) Tumor cells may be epithelioid to spindled. (**c**) Atypical cellular neurothekeoma with significant cellular atypia and pleomorphism. This case also has admixed osteoclast-like giant cells. (**d**) Myxoid variant cellular neurothekeoma. (**e**) Desmoplastic cellular neurothekeoma with cords of tumor cells embedded in a dense collagenous stroma

Fig. 4.29 (continued)

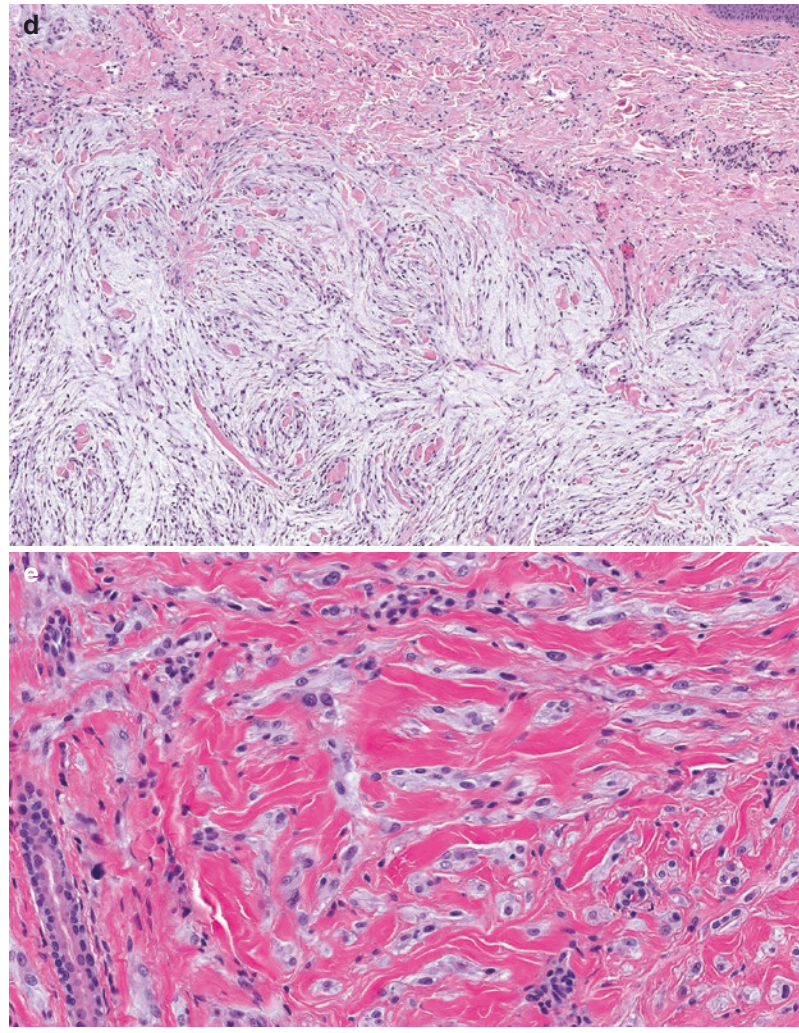


Table 4.29 Key pathologic features: cellular neurothekeoma

Circumscribed dermal tumor
Discrete nests or fascicles of spindled to epithelioid cells often delineated by fibrous septa
Collagenous to focally myxoid stroma
Cases with atypical features including large size (>5 cm), infiltrative growth, high mitotic rate, high cellularity, cytologic atypia, and perineural and lymphovascular invasion have the same prognosis as typical CNTK
NKI-C3, CD10, and PGP9.5 positive. Variable expression of CD68, MiTF (60–68%), and SMA (10–50%). Negative for SOX10, S100 protein, CD34, desmin, pan-cytokeratin, and EMA

more myxoid stroma, and a predominantly spindled morphology and is consistently positive for S100 protein. The tumor nodules of cellular neurothekeoma can bear a striking resemblance to the histiocytoid nodules of plexiform fibrohistiocytic tumor, but the latter has an infiltrative growth pattern and is usually biphasic with histiocytoid nodules and fascicles of spindled cells. Benign fibrous histiocytoma has peripheral collagen trapping and epidermal hyperplasia and does not have a nested growth pattern. Melanocytic tumors are consistently positive for S100 protein and SOX10.

Nodular Fasciitis

Clinical Features

Nodular fasciitis most often occurs in younger patients and affects men and women equally. It typically presents as a solitary, small, rapidly growing mass of the upper extremity, trunk/chest wall, or head and neck region. A history of antecedent trauma is noted in approximately 50% of patients. Nodular fasciitis of the scalp and underlying skull (i.e., cranial fasciitis) typically occurs in young infants and may be associated with birth trauma in a subset of cases. Intradermal, ossifying, and intravascular variants have also been described. Nodular fasciitis is a benign neoplasm with a low risk of recurrence that often spontaneously regresses. Tumors from the head and neck have a higher risk of recurrence compared with cases arising in other locations.

Pathologic Features

Nodular fasciitis is unencapsulated and variably circumscribed. Most cases arise in the subcutis, but as noted above, cases arising in the dermis and within vessels have been reported (Fig. 4.30a). Dermal cases tend to be relatively circumscribed, but nodular fasciitis arising in the subcutis may extend along subcutaneous septa (Fig. 4.30b). Typically, nodular fasciitis is composed of irregular fascicles of bland, lightly eosinophilic spindle cells with a swirling, so-called tissue culture growth pattern (Fig. 4.30c). Constituent tumor cells have elongated delicate cytoplasmic processes and vesicular nuclei with small nucleoli (Fig. 4.30d). Mitotic figures are frequent, but atypical forms are not seen. The background stroma is frequently myxoid with extravasated erythrocytes and areas of cystic breakdown often being present (Fig. 4.30e). These stromal features are important clues to the diagnosis. Older cases may show hyalinization, and some cases will develop keloidal collagen fibers (Fig. 4.30f). Intravascular forms demonstrated vessels expanded by a proliferation of myofibroblasts similar to conventional nodular fasciitis. Intravascular forms often have numerous osteoclast-type giant cells (Fig. 4.30g). Constituent spindle cells demonstrate a "myofibroblastic" immunophenotype and pattern of staining, namely, membranous (tram-track) accentuation of immunoreactivity with immunohistochemical stains to actins (e.g., SMA, caldesmon, and calponin) (Fig. 4.30h). Previously thought to be a reactive process, nodular fasciitis is now known to be a true neoplasm. Over 90% of cases have a translocation involving *USP*6, the same gene involved in aneurysmal bone cysts (Table 4.30).

Differential Diagnosis

Due to its high cellularity and mitotic activity and sometimes prominent areas of myxoid change, nodular fasciitis can be mistaken for myxofibrosarcoma. Myxofibrosarcoma has a greater number of atypical hyperchromatic cells, more prominent myxoid stroma, and usually a distinctive curvilinear vasculature with surrounding tumor cell condensation. Cases of nodular fasciitis arising in the dermis can be mistaken for cellular fibrous histiocytoma and dermatofibrosarcoma protuberans. Cellular fibrous histiocytoma has features of conventional benign fibrous histiocytoma, such as peripheral collagen trapping, and lacks the myxoid stroma and cystic degeneration of nodular fasciitis. Dermatofibrosarcoma protuberans has a tighter more storiform growth pattern, contains spindled cells with slender hyperchromatic nuclei, and infiltrates the fat in a diffuse "honeycomb" pattern, rather than following subcutaneous septa. Immunohistochemical stains play little role in the differential diagnosis, as stains such as SMA and CD34 can be positive at least focally in fasciitis and all the lesions considered in the differential diagnosis. In partial samples or difficult cases, FISH to detect *USP6* rearrangement can confirm the diagnosis.

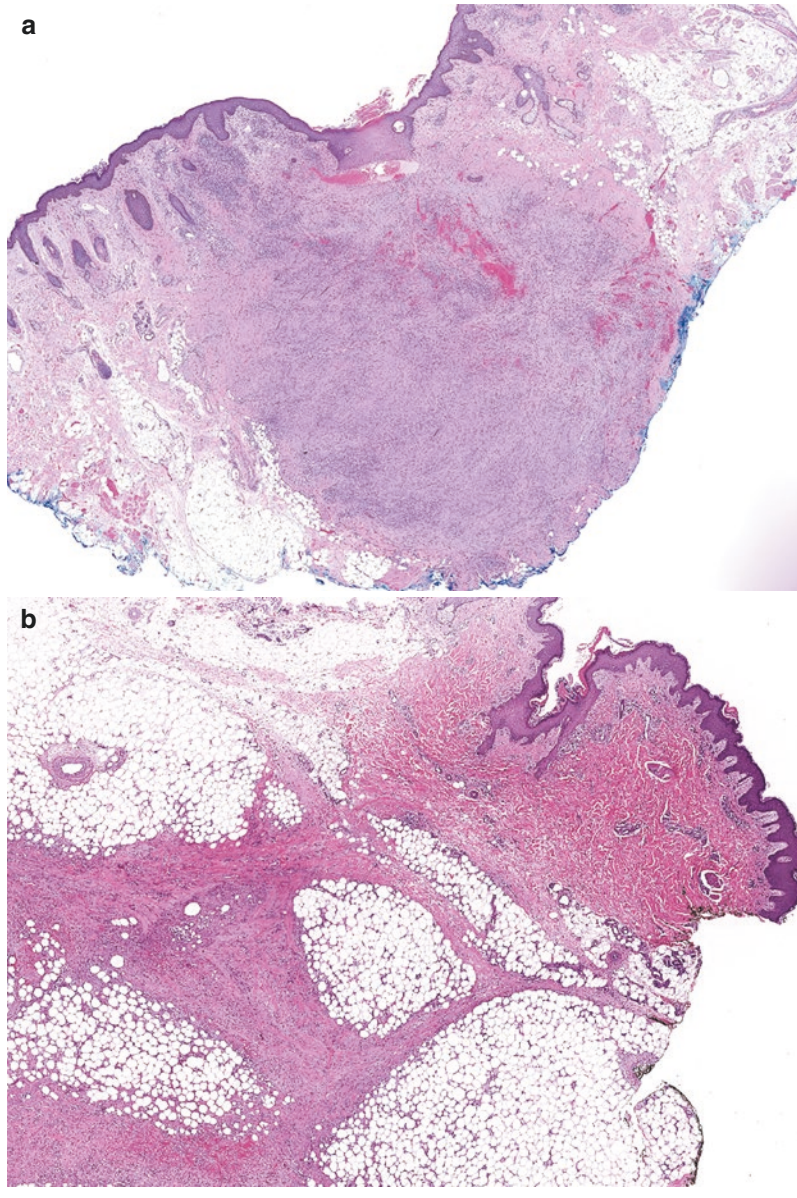
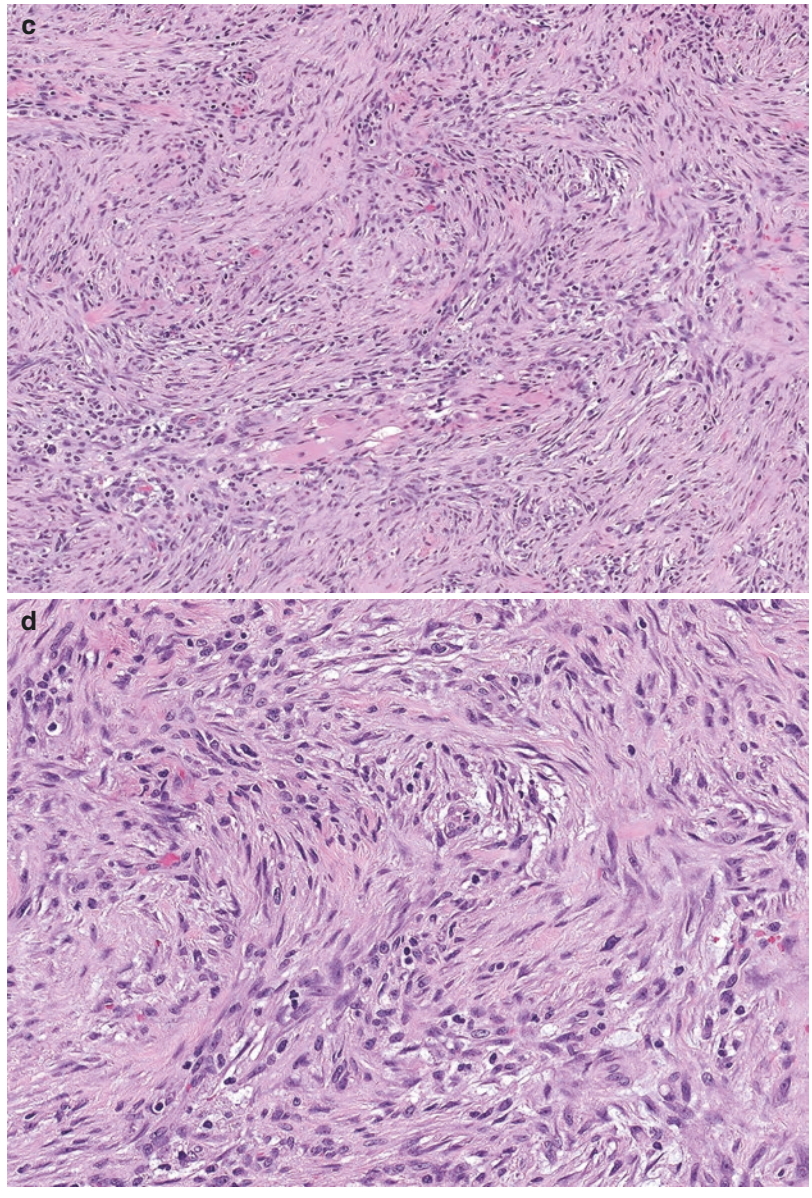


Fig. 4.30 Nodular fasciitis. (**a**) Nodular fasciitis arising in the dermis, showing an unencapsulated but circumscribed proliferation of myofibroblastic spindle cells. (**b**) Cases arising in subcutis tend to extend along fibrous septa. (**c**) Irregular fascicles of lightly eosinophilic spindle cells with a "tissue culture" growth pattern. (**d**) Tumor cells have elongated delicate cytoplasmic processes and vesicular nuclei with small nucleoli. (**e**) Extravasated erythrocytes and myxoid degeneration are helpful diagnostic features. (**f**) An example of nodular fasciitis with keloidal collagen. (**g**) An example of intravascular fasciitis. Note the osteoclast-type giant cells. (**h**) SMA tramtrack pattern of immunoreactivity in nodular fasciitis

Fig. 4.30 (continued)



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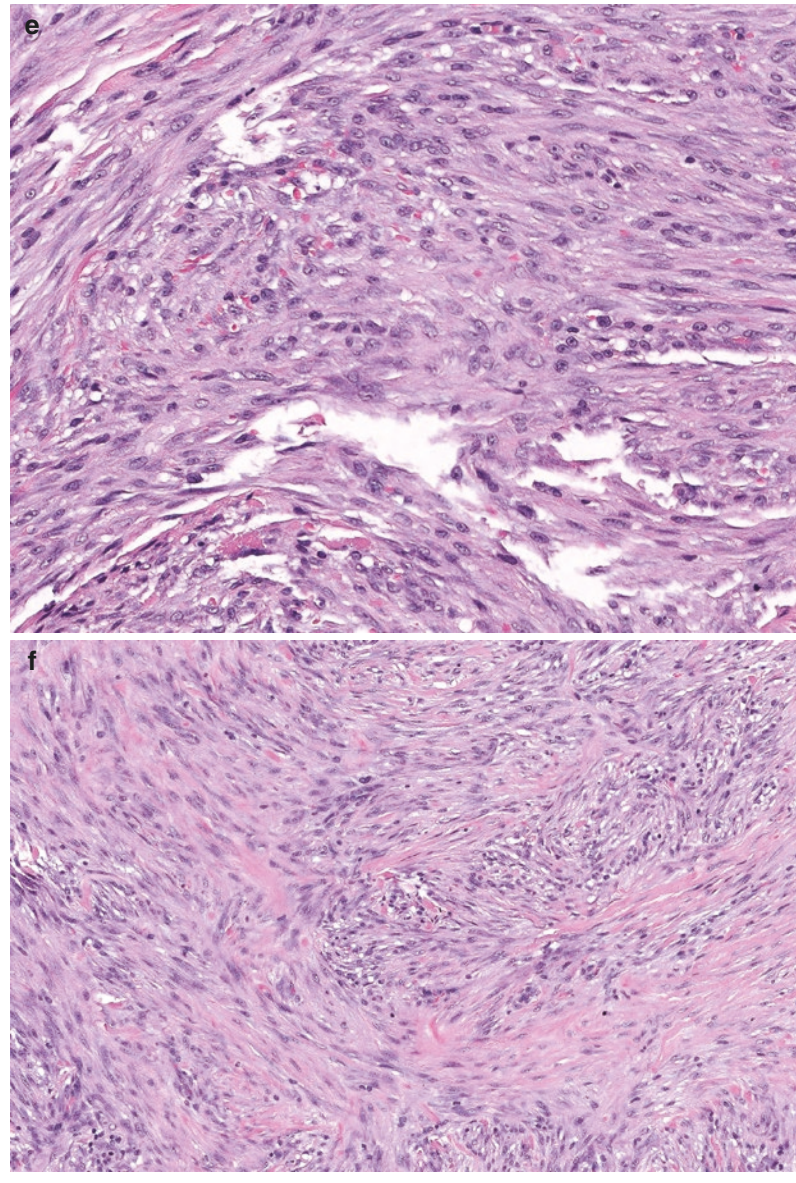

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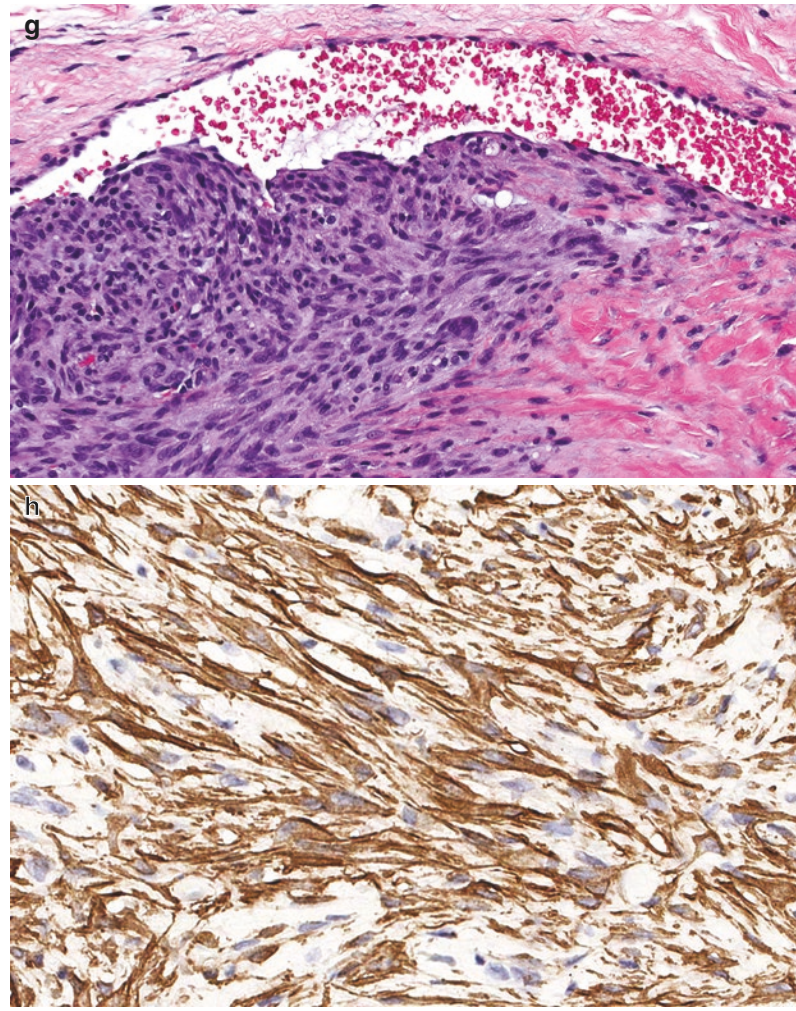

Table 4.30 Key pathologic features: nodular fasciitis

Irregular fascicles of bland lightly eosinophilic spindled cells with a "tissue culture" growth pattern
Mitotically active but no atypical mitoses
Variably myxoid stroma with extravasated erythrocytes and areas of cystic breakdown
Hyalinized stroma with keloid-like collagen in older lesions
Osteoclast-type giant cells may be seen, particularly in intravascular variant
Spindle cells usually positive for actins (SMA, caldesmon, calponin) often in a "tram-track" myofibroblastic pattern
USP6 gene rearrangement

Proliferative Fasciitis

Clinical Features

Proliferative fasciitis, first described by Chung and Enzinger in 1975, has significant clinical overlap with nodular fasciitis including a similar anatomic distribution and association with trauma, but usually presents in a slightly older patient population, with occasional cases presenting in children. Lesions occur in the subcutis of the extremities, trunk, or rarely the head and

neck and are usually less than 5 cm in maximum dimension. Lesions present as firm, but mobile subcutaneous nodules, which may be painful. A history of rapid growth is typical.

Pathologic Features

Most cases of proliferative fasciitis have overlapping features with nodular fasciitis, with a tissue culture-like pattern of spindled cells, myxoid stroma, and extravasation of erythrocytes. The defining histologic feature of proliferative fasciitis is the presence of ganglion-like myofibroblasts interspersed among the spindled cells. These cells have enlarged eccentrically placed nuclei with prominent nucleoli and relatively abundant eosinophilic cytoplasm (Fig. 4.31a and b). Interestingly, pediatric cases may demonstrate a more diffuse, sheetlike growth pattern of ganglion-like myofibroblasts, sometimes with focal areas of necrosis (Fig. 4.31c). Proliferative fasciitis is usually immunoreactive for SMA ("tram-track") and sometimes focally for desmin. Rearrangement of *USP6* has not been identified to date (Table 4.31).

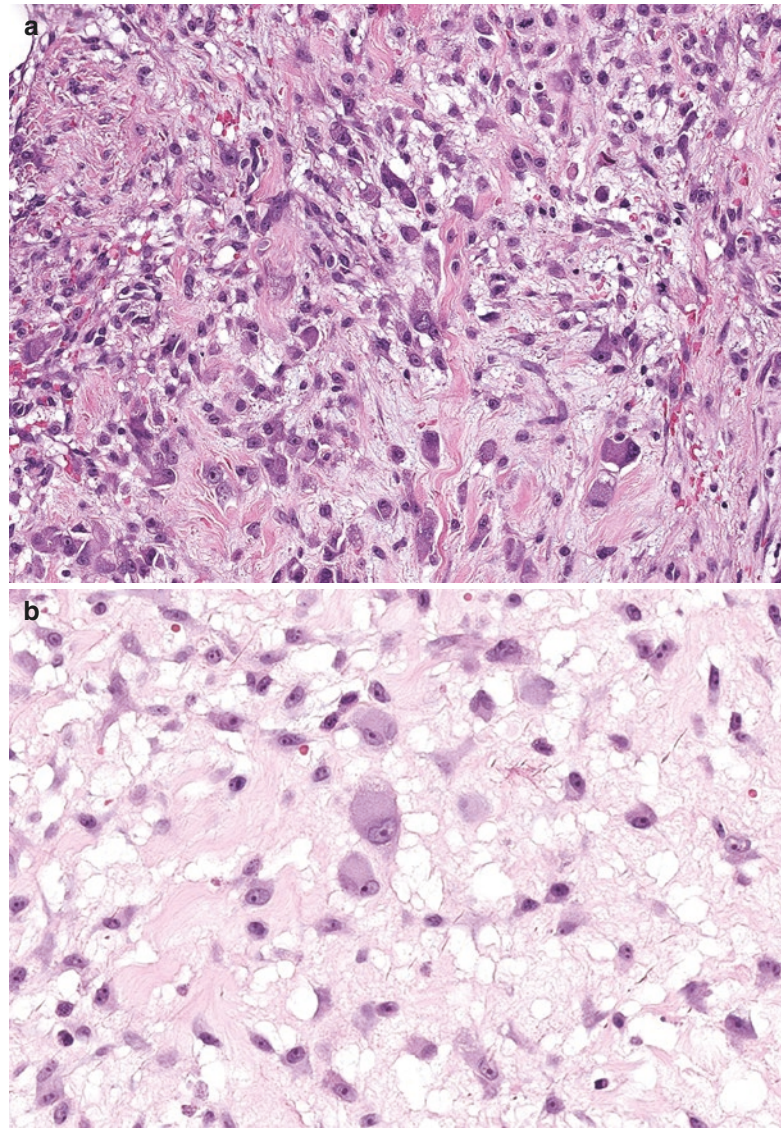

Fig. 4.31 Proliferative fasciitis. (**a**) Overlapping histologic features with nodular fasciitis including spindled myofibroblastic cells and tissue culture-like architecture. Note scattered ganglion-like myofibroblasts. (**b**) High-power view of ganglion-like cells, the defining feature of proliferative fasciitis. (**c**) Pediatric cases may have a diffuse, sheetlike growth of ganglion-like myofibroblasts. Necrosis may also be focally present

Fig. 4.31 (continued)

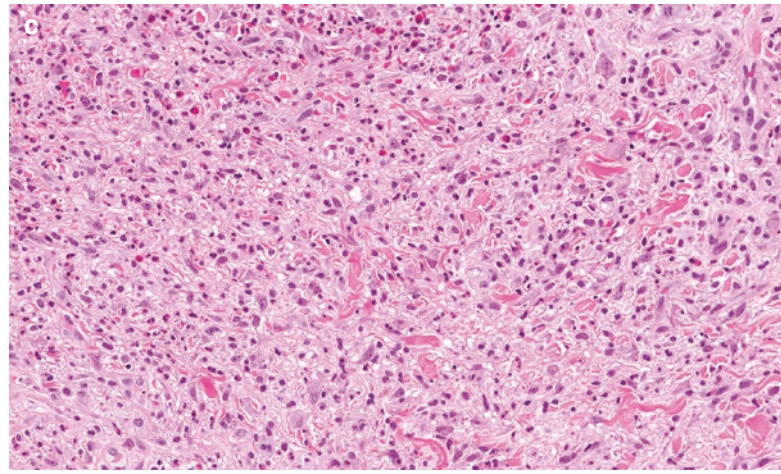

Table 4.31 Key pathologic features: proliferative fasciitis

Overlapping features with nodular fasciitis, including tissue culture-like pattern of spindled cells, myxoid stroma, and extravasation of erythrocytes
Interspersed ganglion-like myofibroblasts are a defining feature
Pediatric cases may have sheetlike growth of ganglion-like cells and foci of necrosis

Differential Diagnosis

The differential of proliferative fasciitis overlaps with the differential diagnosis of nodular fasciitis, as discussed above. The same comments are applicable to proliferative fasciitis. In cases with numerous ganglion-like myofibroblasts, the differential diagnosis can include metastatic melanoma, anaplastic large cell lymphoma, myxoinflammatory fibroblastic sarcoma, epithelioid sarcoma, and, in pediatric cases, rhabdomyosarcoma. With the exception of myxoinflammatory fibroblastic sarcoma, all of the entities in the differential diagnosis can be sorted out with a carefully selected panel of immunohistochemical stains, including S100 protein (melanoma), CD30 (anaplastic large cell lymphoma), epithelioid sarcoma (AE1/3 and INI1), and myogenin (rhabdomyosarcoma). The degree of cytologic atypia and extent of the associated inflammatory infiltrate seen in myxoinflammatory fibroblastic sarcoma exceeds that typically seen in proliferative fasciitis.

Ischemic Fasciitis

Clinical Features

Ischemic fasciitis (also known as decubital ischemic fasciitis or atypical decubital fibroplasia) usually occurs at sites of intermittent pressure-induced ischemia, most commonly in soft tissue overlying bony prominences (e.g., sacrum, hip, shoulder, elbow). It is usually seen in elderly and debilitated patients, but presentation in younger patients is increasingly recognized, especially in cases involving the elbows.

Pathologic Features

Ischemic fasciitis involves the subcutis and demonstrates a characteristic zonal pattern, with central fibrinoid necrosis, adjacent loose myxoid stroma, and a surrounding proliferation of myofibroblastic cells similar to those of nodular fasciitis with admixed ganglion-like myofibroblasts (Fig. 4.32a). A reactive, thin-walled vascular proliferation is also commonly present surrounding the zone of fibrinoid necrosis (Fig. 4.32b). A subset of the reactive myofibroblasts can demonstrate significant hyperchromasia and pleomorphism (Fig. 4.32c), leading to a misdiagnosis of a pleomorphic sarcoma. Similar to other forms of nodular fasciitis, immunoreactivity for SMA is common. Rearrangement of *USP6* is not

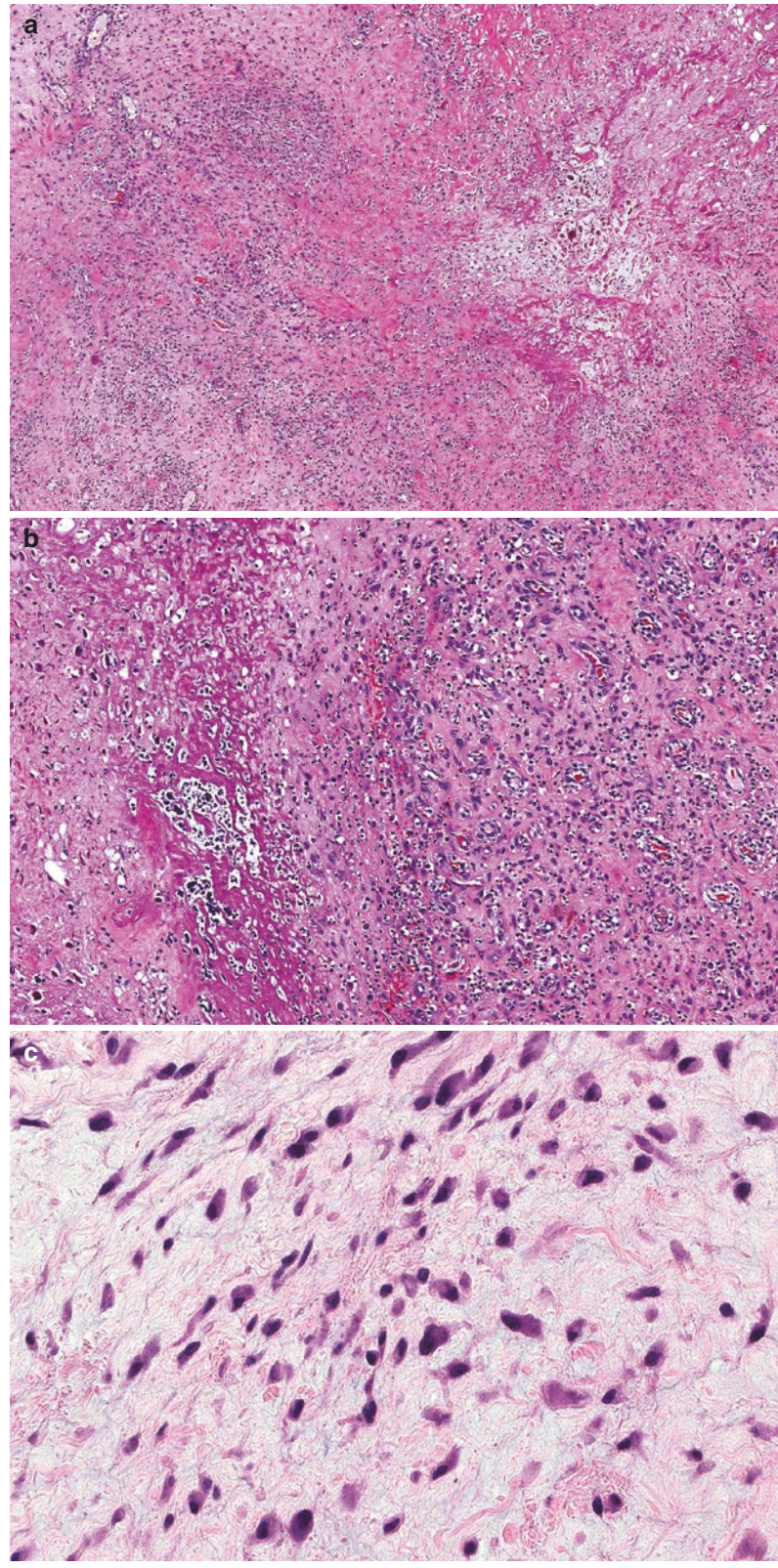

Fig. 4.32 Ischemic fasciitis. (**a**) A reactive spindle cell proliferation with a zonal pattern including a central zone of fibrinoid necrosis surrounded by reactive myofibroblasts. (**b**) Reactive thin-walled vascular proliferation around a zone of fibrinoid necrosis. (**c**) Myofibroblasts with significant hyperchromasia and pleomorphism may be mistaken for evidence of a sarcoma

Table 4.32 Key pathologic features: ischemic fasciitis

Characteristic zonal histology
Central fibrinoid necrosis, adjacent loose myxoid stroma surrounded by a proliferation of myofibroblastic spindle cells
Scattered admixed atypical ganglion-like myofibroblasts

a feature. However, recently novel t(1;2)(p36.1;q23) and t(7;19)(q32;q13.3) chromosomal translocations have been identified in a single case of ischemic fasciitis, suggesting a possible clonal pathogenetic link. The clinical significance of these findings remains to be determined (Table 4.32).

Differential Diagnosis

Ischemic fasciitis is most frequently confused with myxofibrosarcoma and undifferentiated pleomorphic sarcoma. Both of these entities have greater nuclear atypia and lack the distinct zonation of ischemic fasciitis. Immunohistochemistry plays no role in resolving the differential diagnosis.

Fibroma of Tendon Sheath

Clinical Features

Fibroma of tendon sheath (FTS) is a myofibroblastic proliferation related to nodular fasciitis, which arises in tenosynovial soft tissues. Most FTS arise in the upper extremities, with the first three fingers being the most frequent sites of involvement. FTS in the knee, elbow, and wrist have been rarely reported. Affected patients are typically in the second through fifth decades of life. FTS is a benign lesion, which may locally recur in approximately 20–25% of cases, but does not metastasize.

Pathologic Features

Lesions are slow-growing, small (≤3 cm), firm, well-circumscribed nodules typically attached, or directly adjacent, to tendon sheaths. Cleft-like spaces are often seen at the periphery (Fig. 4.33a). Most FTS are hypocellular and contain myofibroblastic spindle cells with elongated, tapered nuclei with indistinct eosinophilic cytoplasmic processes embedded in an eosinophilic hyalinized stroma (Fig. 4.33b). Most lesions have a low mitotic rate and lack significant cytologic atypia. A pleomorphic variant has been described in which a significant level of nuclear hyperchromasia and pleomorphism contrasts with the generally low mitotic activity seen in these lesions as a whole; a degenerative phenomenon has been suggested to reconcile these disparate features (Fig. 4.33c). In newly eruptive lesions, the hyalinized areas alternate with foci more typical of nodular fasciitis, including foci with extensive myxoid change and tissue culture-like architecture, as well as extravasated red cells (Fig. 4.33d). Older lesions are more fibrotic and paucicellular (Fig. 4.33e). In some lesions the tumor has zones of increased cellularity and a more fascicular growth pattern (cellular fibroma of tendon sheath) (Fig. 4.33f). Some lesions contain multinucleated osteoclast-type giant cells, but other secondary elements such as hemosiderin and foam cells are not noted. Similar to nodular fasciitis and related lesions, constituent cells express smooth muscle markers in a reactive tram-track pattern (SMA, caldesmon, and calponin), but are negative for desmin. *USP6* rearrangements have been reported in cellular fibroma of tendon sheath, but not other variants. These lesions are benign but may recur after incomplete excision (Table 4.33).

Differential Diagnosis

Hypocellular collagenized lesions are usually very characteristic and rarely confused with other entities. More cellular variants can resemble classic nodular fasciitis or a cellular fibrous histiocytoma (dermatofibroma). Tenosynovial giant cell tumor has a similar anatomic distribution, but these lesions tend to have more rounded cells, as opposed to the spindled cells seen in FTS. Unlike FTS, osteoclast-type giant cells and other secondary elements, such as xanthoma cells and hemosiderin-laden macrophages, are common in

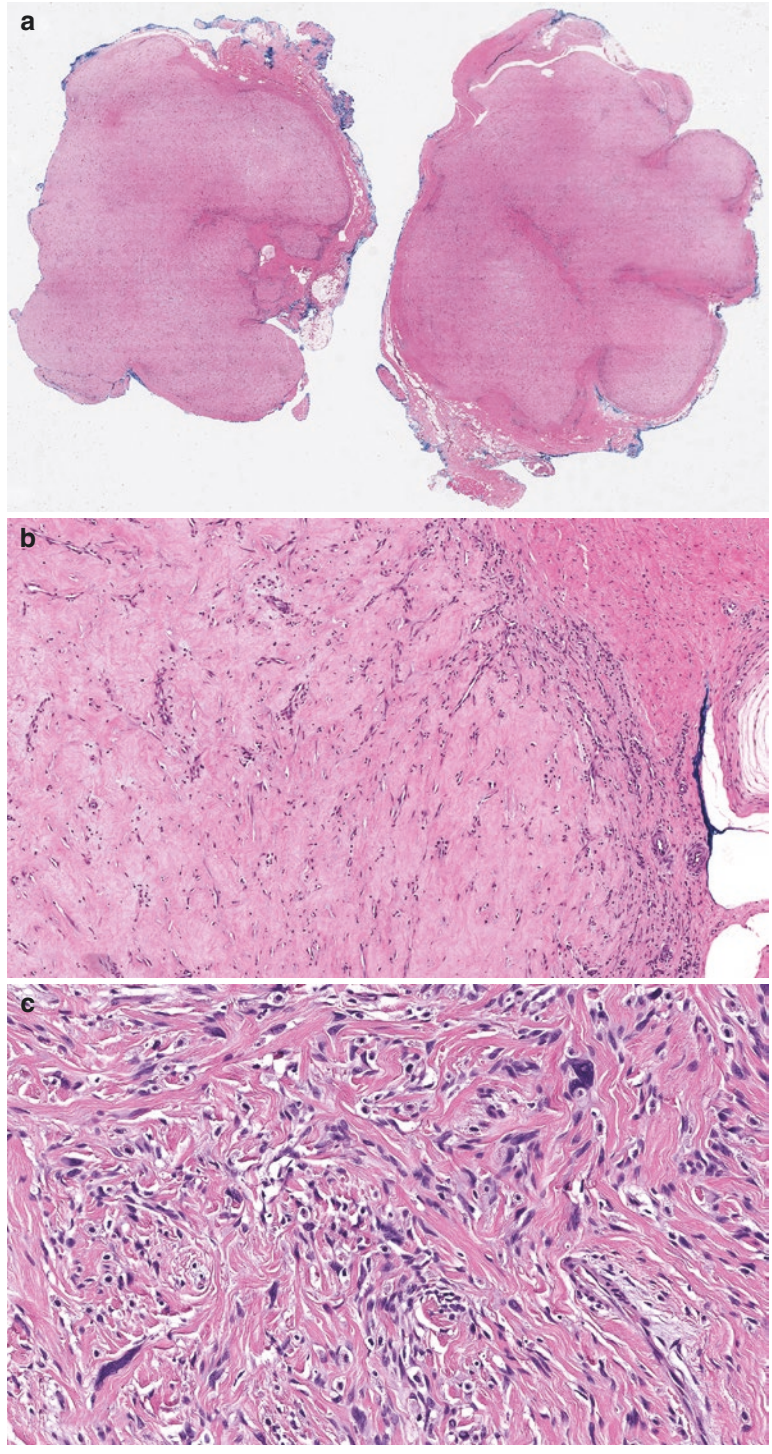

Fig. 4.33 Fibroma of tendon sheath. (**a**) Low-power view illustrating the multinodular architecture of fibroma of tendon sheath. (**b**) A hypocellular lesion composed of myofibroblastic spindle cells with elongated, tapered nuclei with indistinct eosinophilic cytoplasmic processes embedded in a hyalinized stroma. (**c**) Pleomorphic fibroma of tendon sheath is likely due to a degenerative phenomenon resulting in nuclear hyperchromasia and pleomorphism. (**d**) Extensive myxoid change and tissue culture-like architecture, as well as extravasated red cells in a newly eruptive lesion. (**e**) Extensive fibrosis typical of an older lesion. (**f**) Cellular fibroma of tendon sheath showing zones of increased cellularity

Fig. 4.33 (continued)

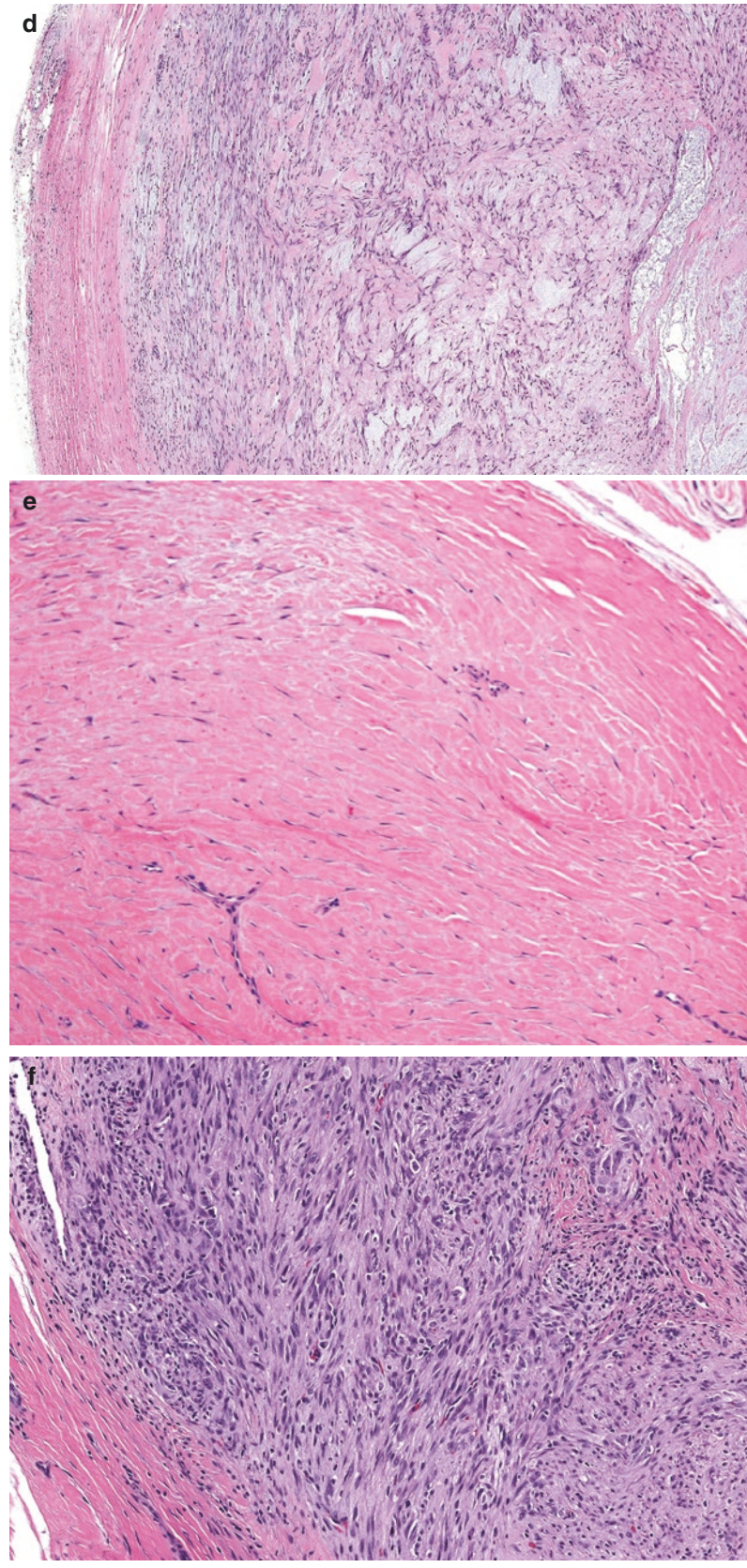

Table 4.33 Key pathologic features: fibroma of tendon sheath

Bland spindle cells in a heavily collagenized matrix surrounding slit-like vessels
Increased cellularity and nuclear atypia in cellular and pleomorphic variants, respectively
Tram-track immunoreactivity for actins but not desmin
Translocations involving the long t(2:11) (q31–32; q12), a finding shared with giant cell tumor of tendon sheath, but showing different break points
USP6 gene rearrangements seen in a subset of cellular fibromas of tendon sheath, but not other variants

tenosynovial giant cell tumor. Finally, pleomorphic variants of FTS can be confused with pleomorphic sarcomas, which in general demonstrate greater mitotic activity, cellularity, and pleomorphism.

Calcifying Fibrous Pseudotumor

Clinical Features

Calcifying fibrous pseudotumor is a rare benign soft tissue pseudotumor with slight female predominance that typically occurs in children and young adults. Tumors usually present as slowly growing painless soft tissue masses in the extremities, thorax, abdomen, or head and neck, although tumors can occur at essentially any site in the body, including visceral sites, such as the gastrointestinal tract. It shares several clinical and morphologic features with IgG4-related sclerosing diseases, although this link remains unsubstantiated. Radiographic imaging may demonstrate a soft tissue mass with intralesional mineralization. Tumors demonstrate indolent clinical behavior, with only rare local recurrences after surgical excision.

Pathologic Features

Grossly, tumors are unencapsulated, but circumscribed solid superficial or deep soft tissue masses. Microscopically, tumors are relatively circumscribed, hypocellular, and comprised of bland-appearing fibroblastic spindle cells within densely collagenous stroma. Variable mixed chronic inflammatory cells, including lymphocytes and plasma cells, are present, and characteristic focal to diffuse dystrophic and/or psammomatous calcifications are noted (Fig. 4.34a). Spindle cells show variable SMA, muscle-specific actin, desmin, CD34, and FXIIIa staining but are negative for S100 protein, pancytokeratin, and ALK expression. The presence of IgG4-positive plasma cells in these tumors, particularly those arising in the GI tract, has raised the possibility that they represent a variant in the spectrum of IgG4-related sclerosing diseases. A recent study identified novel deleterious mutations in *ZN717*, *FRG1*, and *CDC27* genes as well as significant copy number losses on eight chromosomes with a large loss common to all samples on chromosome 6. These mutations deleteriously altered coding domains in a manner predicted to be damaging to protein function, suggesting a role in CFTP tumorigenesis (Table 4.34).

Differential Diagnosis

The differential diagnosis for calcifying fibrous pseudotumor includes burned-out nodular fasciitis, fibromatosis, inflammatory myofibroblastic tumor, fibro-osseous pseudotumor of digits, and calcifying aponeurotic fibroma. In general, late-stage nodular fasciitis still has more cellular areas than calcifying fibrous pseudotumor and does not typically show prominent calcifications. Fibromatosis generally demonstrates prominent fascicular growth and only rarely shows calcifications. Inflammatory myofibroblastic tumor (IMT) is an important differential diagnostic consideration, as it can show significant morphologic overlap with calcifying fibrous pseudotumor, although in general, inflammatory myofibroblastic tumors are more cellular and show a more prominent inflammatory infiltrate; documentation of an *ALK* gene rearrangement or ALK protein expression argues against the diagnosis of calcifying fibrous pseudotumor and in favor of IMT. Finally, depending on the clinical features, fibro-osseous pseudotumor of digits and/or calci-

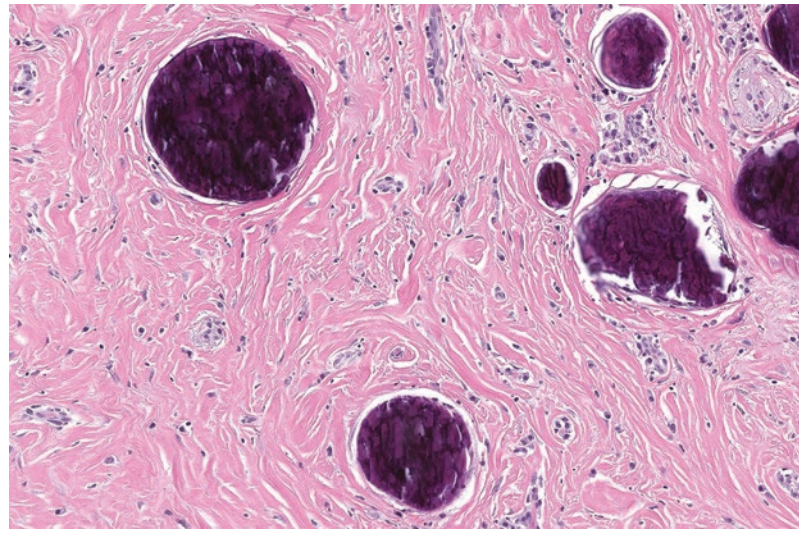

Fig. 4.34 Calcifying fibrous pseudotumor. Calcified deposits and fibroblastic cells within a fibrous stroma in a case of calcifying fibrous pseudotumor

Table 4.34 Key pathologic features: calcifying fibrous pseudotumor

Well-circumscribed mass composed of hyalinized fibrosclerotic tissue
Variable inflammatory infiltrate composed of lymphocytes and plasma cells
Psammomatous calcifications are a characteristic feature
Scattered, bland fibroblastic, and myofibroblastic spindle cells
Spindle cells show variable immunoreactivity for SMA, MSA, CD34, and FXIIIa
IgG4-positive plasma cells present in a subset

fying aponeurotic fibroma may enter the differential diagnosis of calcifying fibrous pseudotumor. The presence of maturing osteoid, osteoblastic rimming, and admixed multinucleated osteoclast-like giant cells, as well as the distinctive clinical presentation, suggests fibro-osseous pseudotumor of digits, while central cartilage formation and calcification favors a diagnosis of calcifying aponeurotic fibroma.

Fibroosseous Pseudotumor of Digits

Clinical Features

Fibro-osseous pseudotumor of digits (FOPT) is a form of heterotopic ossification originally described under the name "florid reactive periostitis of the tubular bones of the hands and feet" in 1981 and renamed FOPT in 1986. It has been likened to myositis ossificans and presents as a small, painful papule on the second or third finger. It is more common in women and young adults and has been associated with repetitive trauma secondary to manual labor. Tumors usually present as enlarging painful and/or swollen soft tissue masses. Radiographic imaging may demonstrate a vague soft tissue mass with disorganized intralesional mineralization, and the tumor may appear to involve the underlying cortical bone (Fig. 4.35a). Tumors show benign clinical behavior without local recurrence after surgical excision.

Pathologic Features

The tumors are unencapsulated but circumscribed solid superficial soft tissue masses. Microscopically, tumors are typically hypercellular and comprised of plump fibroblastic spindle cells with moderate eosinophilic cytoplasm, enlarged and slightly irregular vesicular nuclei, and inconspicuous nucleoli. Tumor cells are arranged haphazardly and in short fascicles within variable fibromyxoid stroma. Admixed foci of osteoid formation with osteoblastic rimming, patchy calcification, and scattered multinucleated osteoclast-like giant cells are present (Fig. 4.35b). Although mitotic activity may be present, there is no significant cytologic atypia

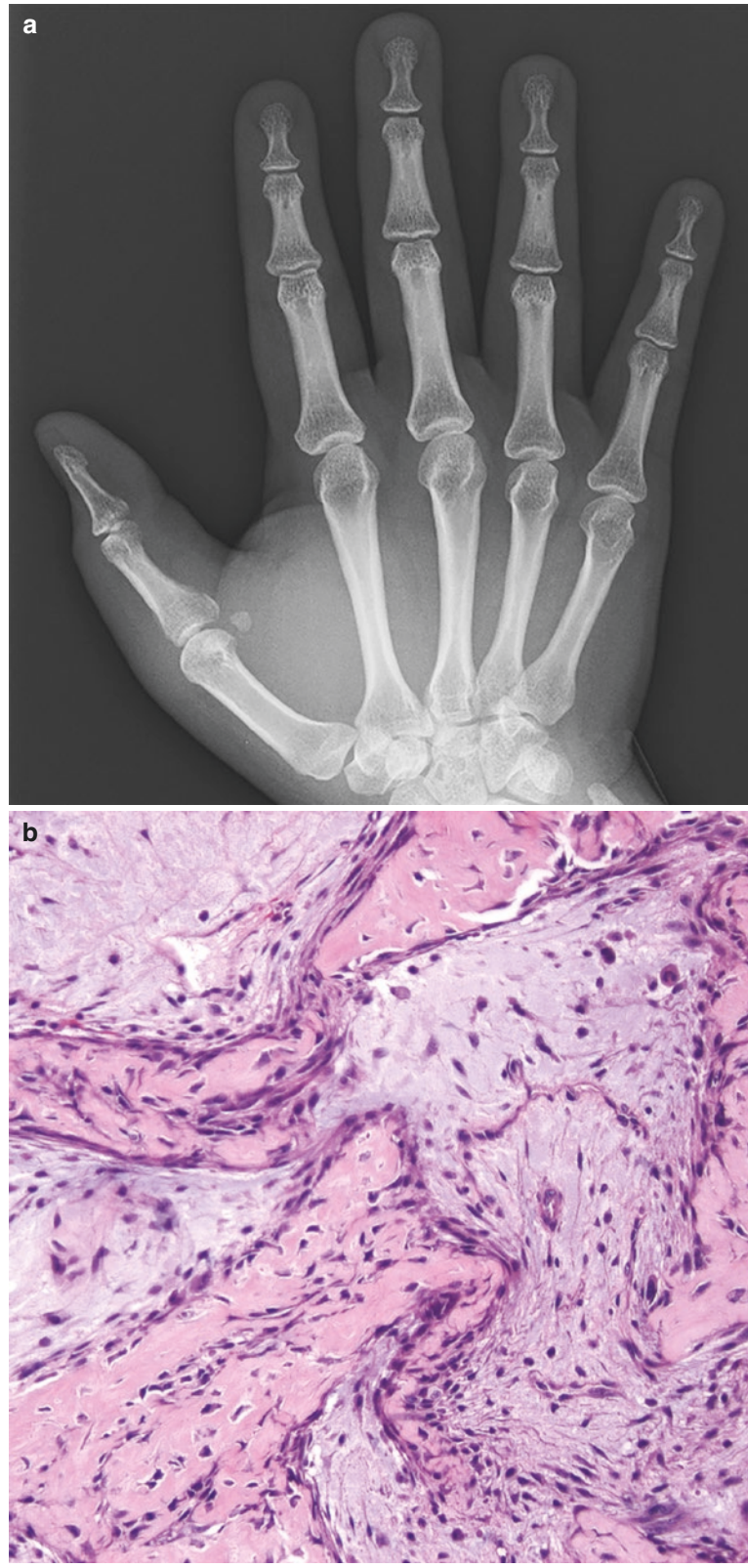

Fig. 4.35 Fibro-osseous tumor of digits. (**a**) Radiograph demonstrating a vague soft tissue mass with disorganized intralesional mineralization between the thumb and index finger. The tumor may appear to involve the underlying cortical bone. (**b**) Plump fibroblasts within a fibromyxoid stroma with osteoid formation. (Images courtesy of Dr. David Lucas, University of Michigan)

Table 4.35 Key pathologic features: fibro-osseous pseudotumor of digits

Digital subcutaneous multinodular lesion extending into fibrous tissues
Cellular proliferation of haphazardly arranged myofibroblastic cells
Foci of osteoid and bone formation with osteoblastic rimming, patchy calcification, and scattered multinucleated osteoclast-like giant cells
Spindle cells express SMA ("tram-track" pattern) but are negative for desmin, S100, CD34, and pan-cytokeratin
Subset demonstrate *USP6* rearrangement

or necrosis. The spindle cells express SMA, but are negative for desmin, S100, CD34, and pan-cytokeratin expression. In a recent study, four of five cases of FOPT demonstrated *USP6* rearrangements placing these lesions in the group of transient neoplasms including nodular fasciitis and myositis ossificans (Table 4.35).

Differential Diagnosis

The differential diagnosis of fibro-osseous pseudotumor of digits includes subungual exostosis, soft tissue giant cell tumor, giant cell tumor of bone, and theoretically, osteosarcoma. Of these entities, subungual exostosis is the only one with significant clinical overlap involving presentation in the digits. Subungual exostosis is usually less cellular, and radiographs will demonstrate origin from the underlying bone. Presentation of the other entities in the digits is exceptional. Both giant cell tumor of bone and most cases of osteosarcoma arise from bone. Osseous and extraskeletal osteosarcoma typically exhibit a much greater degree of cytologic atypia.

Selected References

1. Aceñero MJ, Vorwald PW, Yamauchi SC. Calcifying fibrous pseudotumor affecting the retroperitoneum: could it be a new entity within the spectrum of IgG-4 sclerosing disease? Virchows Arch. 2010;456(6):719–21.
2. Agaimy A, Michal M, Giedl J, Hadravsky L, Michal M. Superficial acral fibromyxoma: clinicopathological, immunohistochemical, and molecular study of 11 cases highlighting frequent Rb1 loss/deletions. Hum Pathol. 2017;60:192–8. PMID:27825811.
3. Agaram NP, Zhang L, Sung YS, Chen CL, Chung CT, Antonescu CR, Fletcher CD. Recurrent NTRK1 Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors. Am J Surg Pathol. 2016;40(10):1407–16.
4. Al-Ibraheemi A, Martinez A, Weiss SW, Kozakewich HP, Perez-Atayde AR, Tran H, Parham DM, Sukov WR, Fritchie KJ, Folpe AL. Fibrous hamartoma of infancy: a clinicopathologic study of 145 cases, including 2 with sarcomatous features. Mod Pathol. 2017;30(4):474–85.
5. Allen PW. Nodular fasciitis. Pathology. 1972;4(1):9–26.
6. Allen PW, Dymock RB, MacCormac LB. Superficial angiomyxomas with and without epithelial components. Report of 30 tumors in 28 patients. Am J Surg Pathol. 1988;12(7):519–30.
7. Al-Zaid T, Wang WL, Lopez-Terrada D, Lev D, Hornick JL, Hafeez-Diwan A, Fletcher CD, Lazar AJ. Pleomorphic fibroma and dermal atypical lipomatous tumor: Are they related? J Cutan Pathol. 2013;40(4):378–84.
8. Amaravati R. Rare malignant transformation of a calcifying aponeurotic fibroma. J Bone Joint Surg Am. 2002;84-A(10):1889, author reply 1889.
9. Balachandran K, Allen PW, MacCormac LB. Nuchal fibroma. A clinicopathological study of nine cases. Am J Surg Pathol. 1995;19(3):313–7. PMID:7872429.
10. Bansal C, Stewart D, Li A, et al. Histologic variants of fibrous papule. J Cutan Pathol. 2005;32:424–8. 15953376.
11. Barnhill RL, Mihm MC Jr. Cellular neurothekeoma. A distinctive variant of neurothekeoma mimicking nevomelanocytic tumors. Am J Surg Pathol. 1990;14:113–20.
12. Beerman H. Lipid diseases as manifested in the skin. Med Clin N Am. 1951;35(2):433–56.
13. Bertoni F, Unni KK, Beabout JW, et al. Malignant giant cell tumor of the tendon sheaths and joints (malignant pigmented villonodular synovitis). Am J Surg Pathol. 1997;21(2):153–63.
14. Boland JM, Folpe AL, Hornick JL, et al. Clusterin is expressed in normal synoviocytes and in tenosynovial giant cell tumors of localized and diffuse types: diagnostic and histogenetic implications. Am J Surg Pathol. 2009;33(8):1225–9.
15. Brazzelli V, Rivetti N, Carugno A, Barruscotti S, Croci GA, Perani G, Borroni G. Eruptive xanthomas after extensive tattooing: a case report and literature review. G Ital Dermatol Venereol. 2015;150(6):770–1.Wilkes LL. Tendon xanthoma in type IV hyperlipoproteinemia. South Med J [Case Reports]. 1977;70(2):254–5.
16. Briganti A, Salonia A, Deho F, Zanni G, Rokkas K, Rigatti P, et al. Peyronie's disease: a review. Curr Opin Urol. 2003;13(5):417–22.
17. Bürgi J, Kunz B, Abrami L, Deuquet J, Piersigilli A, Scholl-Bürgi S, Lausch E, Unger S, Superti-Furga A,

Bonaldo P, et al. CMG2/ANTXR2 regulates extracellular collagen VI which accumulates in hyaline fibromatosis syndrome. Nat Commun. 2017;8:15861. https://doi.org/10.1038/ncomms15861.
18. Busam KJ, Mentzel T, Colpaert C, Barnhill RL, Fletcher CD. Atypical or worrisome features in cellular neurothekeoma: a study of 10 cases. Am J Surg Pathol. 1998;22:1067–72.
19. Calonje E, Mentzel T, Fletcher CD, Path MRC. Cellular benign fibrous histiocytoma. Clinicopathologic analysis of 74 cases of a distinctive variant of cutaneous fibrous histiocytoma with frequent recurrence. Am J Surg Pathol. 1994;18(7):668–76.
20. Calonje E, Guerin D, McCormick D, Fletcher CD. Superficial angiomyxoma: clinicopathologic analysis of a series of distinctive but poorly recognized cutaneous tumors with tendency for recurrence. Am J Surg Pathol. 1999;23(8):910–7.
21. Carter JM, Wang X, Dong J, Westendorf J, Choux MM, Oliveira AM. USP6 genetic arrangements in cellular fibroma of tendon sheath. Mod Pathol. 2016;29(8):865–9.
22. Cassier PA, Gelderblom H, Stacchiotti S, Thomas D, Maki RG, Kroep JR, van der Graaf WT, Italiano A, Seddon B, Dômont J, Bompas E, Wagner AJ, Blay JY. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649–55.
23. Chaudhry IH, Kazakov DV, Michal M, Mentzel T, Luzar B, Calonje E. Fibro-osseous pseudotumor of the digit: a clinicopathological study of 17 cases. J Cutan Pathol. 2010;37(3):323–9.
24. Chung EB, Enzinger FM. Proliferative fasciitis. Cancer. 1975;36(4):1450–8.
25. Chung EB, Enzinger FM. Fibroma of tendon sheath. Cancer. 1979;44(5):1945–54.
26. Coffin CM, Hornick JL, Zhou H, Fletcher CDM. Gardner fibroma: A clinical, pathologic, and immunohistochemical analysis of 45 patients with 57 fibromas. Am J Surg Pathol. 2007;31(3):410–6.
27. Cohen BA, Hood A. Xanthogranuloma: report on clinical and histologic findings in 64 patients. Pediatr Dermatol. 1989;6(4):262–6.
28. Cullen D, Díaz Recuero JL, Cullen R, Rodríguez Peralto JL, Kutzner H, Requena L. Superficial acral fibromyxoma: report of 13 cases with new immunohistochemical findings. Am J Dermatopathol. 2017;39(1):14–22. PMID:28045748.
29. Darling TN, Skarulis MC, Steinberg SM, et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol. 1997;133:853–7.
30. de Feraudy S, Fletcher CDM. Intradermal nodular fasciitis: a rare lesion analyzed in a series of 24 cases. Am J Surg Pathol. 2010;34(9):1377–81.
31. de Feraudy S, Fletcher CD. Fibroblastic connective tissue nevus: a rare cutaneous lesion analyzed in a series of 25 cases. Am J Surg Pathol. 2012;36:1509.
32. de Silva MV, Reid R. Myositis ossificans and fibroosseous pseudotumor of digits: a clinicopathologic review of 64 cases with emphasis on diagnostic pitfalls. Int J Surg Pathol. 2003;11:187–95.
33. De Wever I, Dal Cin P, Fletcher CD, Mandahl N, Mertens F, Mitelman F, et al. Cytogenetic, clinical, and morphologic correlations in 78 cases of fibromatosis: a report from the CHAMP Study Group. Chromosomes and Morphology. Mod Pathol. 2000;13(10):1080–5. PMID:11048801.
34. Dehner LP. Juvenile xanthogranulomas in the first two decades of life: a clinicopathologic study of 174 cases with cutaneous and extracutaneous manifestations. Am J Surg Pathol. 2003;27(5):579–93.
35. Denadai R, Bertola DR, Stelini RF, et al. Additional thoughts about juvenile hyaline fibromatosis and infantile systemic hyalinosis. Adv Anat Pathol. 2012;19(3):191–2; author reply 192.
36. Downey C, Requena L, Bagué S, Sánchez Martínez MÁ, Lloreta J, Baselga E. Agminated fibroblastic connective tissue nevus: a new clinical presentation. Pediatr Dermatol. 2016;33(4):e240–3.
37. Doyle LA, Fletcher CD. Metastasizing "benign" cutaneous fibrous histiocytoma: a clinicopathologic analysis of 16 cases. Am J Surg Pathol. 2013;37(4):484–95.
38. Doyle LA, Marino-Enriquez A, Fletcher CDM, Hornick JL. ALK rearrangement and overexpression in epithelioid fibrous histiocytoma. Mod Pathol. 2015;28:904–12.
39. Dupree WB, Enzinger FM. Fibro-osseous pseudotumor of the digits. Cancer. 1986;58:2103–9.
40. Edgar MA, Lauer SR, Bridge JA, et al. Soft tissue angiofibroma: report of 2 cases of a recently described tumor. Hum Pathol. 2013;44(3):438–41.
41. Erickson-Johnson MR, Chou MM, Evers BR, et al. Nodular fasciitis: a novel model of transient neoplasia induced by MYH9-USP6 gene fusion. Lab Investig. 2011;91(10):1427–33.
42. Estela JR, Rico MT, Pérez A, Unamuno B, Garcías J, Cubells L, et al. Dermatofibroma of the face: a clinicopathologic study of 20 cases. Actas Dermosifiliogr. 2014;105(2):172–7. PMID:24275565.
43. Evans HL. Desmoplastic fibroblastoma. A report of 7 cases. Am J Surg Pathol. 1995;19:1077–81.
44. Evans HL. Multinucleated giant cells in plantar fibromatosis. Am J Surg Pathol. 2002; 26(2):244–248. PMID:11812947.
45. Fanti PA, Dika E, Piraccini BM, Infusino SD, Baraldi C, Misciali C. Superficial acral fibromyxoma: a clinicopathological and immunohistochemical analysis of 12 cases of a distinctive soft tissue tumor with a predilection for the fingers and toes. G Ital Dermatol Venereol. 2011;146(4):283–7.
46. Fetsch JF, Miettinen M. Calcifying aponeurotic fibroma: a clinicopathologic study of 22 cases arising in uncommon sites. Hum Pathol. 1998;29(12):1504–10. PMID:9865839.
47. Fetsch JF, Miettinen M, Laskin WB, et al. A clinicopathologic study of 45 pediatric soft tissue tumors

with an admixture of adipose tissue and fibroblastic elements, and a proposal for classification as lipofibromatosis. Am J Surg Pathol. 2000;24(11):1491–500.
48. Fetsch JF, Laskin WB, Miettinen M. Superficial acral fibromyxoma: a clinicopathologic and immunohistochemical analysis of 37 cases of a distinctive soft tissue tumor with a predilection for the fingers and toes. Hum Pathol. 2001;32(7):704–14.
49. Fetsch JF, Laskin WB, Miettinen M. Palmar-plantar fibromatosis in children and preadolescents: a clinicopathologic study of 56 cases with newly recognized demographics and extended follow-up information. Am J Surg Pathol. 2005;29(8):1095–105.
50. Fetsch JF, Laskin WB, Hallman JR, Lupton GP, Miettinen M. Neurothekeoma: an analysis of 178 tumors with detailed immunohistochemical data and long-term patient follow-up information. Am J Surg Pathol. 2007;31:1103–14.
51. Fletcher CD, Powell G, van Noorden S, et al. Fibrous hamartoma of infancy: a histochemical and immunohistochemical study. Histopathology. 1988;12:65–74.
52. Flucke U, Shepard SJ, Bekers EM, Tirabasco R, van Diest PJ, Creytens D, van Gorp JM. Fibro-osseous pseudotumor of digits- Expanding the spectrum of clonal transient neoplasms harboring *USP6* rearrangement. Ann Diagn Pathol. 2018;35:53–5.
53. Folpe AL, Weiss SW, Fletcher CD, et al. Tenosynovial giant cell tumors: evidence for a desmin-positive dendritic cell subpopulation. Mod Pathol. 1998;11(10):939–44.
54. Frew JW. Multinucleate cell angiohistiocytoma: clinicopathological correlation of 142 cases with insights into etiology and pathogenesis. Am J Dermatopathol. 2015;37:222–8.
55. Fullen DR, Lowe L, Su LD. Antibody to S100a6 protein is a sensitive immunohistochemical marker for neurothekeoma. J Cutan Pathol. 2003;30:118–22.
56. Gauchotte G, Bressenot A, Serradori T, et al. Reactive nodular fibrous pseudotumor: a first report of gastric localization and clinicopathologic review. Gastroenterol Clin Biol. 2009;33(12):1076–81.
57. Gleason BC, Fletcher CD. Deep "benign" fibrous histiocytoma: clinicopathologic analysis of 69 cases of a rare tumor indicating occasional metastatic potential. Am J Surg Pathol. 2008;32(3):354–62.
58. Glusac EJ, Barr RJ, Everett MA, et al. Epithelioid cell histiocytoma. A report of 10 cases including a new cellular variant. Am J Surg Pathol. 1994;18(6):583–90.
59. Guitart J, Bergfeld WF, Tuthill RJ. Fibrous papule of the nose with granular cells: Two cases. J Cutan Pathol. 1991;18:284–7.
60. Hall LD, Ferringer T. The best diagnosis is: Eruptive xanthoma. Cutis. 2012;90(1):12, 15–6.
61. Hanft VN, Shea CR, McNutt NS, Pullitzer D, Horenstein MG, Prieto VG. Expression of CD34 in sclerotic ("plywood") fibromas. Am J Dermatopathol. 2000;22(1):17–21.
62. Hepple R, Kreysel HW. Cutaneous angiomyxoma: a benign neoplasm distinct from cutaneous focal mucinosis. J Am Acad Dermatol. 1995;33(2 Pt 2):352–5.
63. Hernández JL, Rodríguez-Parets JO, Valero JM, Muñoz MA, Benito MR, Hernandez JM, Bullón A. High-resolution genome-wide analysis of chromosomal alterations in elastofibroma. Virchows Arch. 2010;456(6):–681, 7.
64. Heymann WR. Infantile digital fibromatosis. J Am Acad Dermatol. 2008;59(1):122–3.
65. Hill KA, Gonzalez-Crussi F, Omeroglu A, et al. Calcifying fibrous pseudotumor involving the neck of a five-week-old infant. Presence of factor XIIIa in the lesional cells. Pathol Res Pract. 2000;196(7):527–31.
66. Hinds B, Ajello-Perez AD, LeBoit PE, McCalmont TH, North JP. Loss of retinoblastoma in pleomorphic fibroma: an immunohistochemical and genomic analysis. J Cutan Pathol. 2017;44(8):665–761.
67. Hollmann TJ, Bovée JV, Fletcher CD. Digital fibromyxoma (superficial acral fibromyxoma): a detailed characterization of 124 cases. Am J Surg Pathol. 2012;36(6):789–98.
68. Hsieh YJ, Lin YC, Wu YH, Su HY, Billings SD, Hood AF. Subungual pleomorphic fibroma. J Cutan Pathol. 2003;30(9):569–71.
69. Iwata J, Fletcher CD. Lipidized fibrous histiocytoma: clinicopathologic analysis of 22 cases. Am J Dermatopathol. 2000;22(2):126–34.
70. Jain A, Maheshwari V, Alam K, et al. Calcifying fibrous pseudotumor of peritoneum. J Postgrad Med. 2007;53(3):189–90.
71. Jang KS, Oh YH, Han HX, et al. Calcifying fibrous pseudotumor of the pleura. Ann Thorac Surg. 2004;78(6):e87–8.
72. Janssen D, Harms D. Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the Kiel pediatric tumor registry. Am J Surg Pathol. 2005;29(1):21–8.
73. Jiménez-Heffernan JA, Urbano J, Tobio R, et al. Calcifying fibrous pseudotumor: a rare entity related to inflammatory pseudotumor. Acta Cytol. 2000;44(5):932–4.
74. Jin Y, Möller E, Nord KH, et al. Fusion of the AHRR and NCOA2 genes through a recurrent translocation t(5;8)(p15;q13) in soft tissue angiofibroma results in upregulation of aryl hydrocarbon receptor target genes. Genes Chromosomes Cancer. 2012;51(5):510–20.
75. Jumper N, Paus R, Bayat A. Functional histopathology of keloid disease. Histol Histopathol. 2015;30(9):1033–57.
76. Kaddu S, McMenamin ME, Fletcher CD. Atypical fibrous histiocytoma of the skin: clinicopathologic analysis of 59 cases with evidence of infrequent metastasis. Am J Surg Pathol. 2002;26(1):35–46.
77. Kamino H, Jacobson M. Dermatofibroma extending into the subcutaneous tissue. Differential diagnosis

from dermatofibrosarcoma protuberans. Am J Surg Pathol. 1990;14(12):1156–64.
78. Kamino H, Lee JY, Berke A. Pleomorphic fibroma of the skin: a benign neoplasm with cytologic atypia. A clinical pathologic study of 8 cases. Am J Surg Pathol. 1989;13:107–13.
79. Kamino H, Reddy VB, Gero M, Greco MA. Dermatomyofibroma. A benign cutaneous, plaque-like proliferation of fibroblasts and myofibroblasts in young adults. J Cutan Pathol. 1992;19:85.
80. Kan AE, Rogers M. Juvenile hyaline fibromatosis: an expanded clinicopathologic spectrum. Pediatr Dermatol. 1989;6(2):68–75.
81. Kato I, Yoshida A, Ikegami M, Okuma T, Tonooka A, Horiguchi S, Funata N, Kawai A, Goto T, Hishima T, Aoki I, Motoi T. FOS1 immunohistochemistry clarifies distinction between desmoplastic fibroblastoma and fibroma of tendon sheath. Histopathology. 2016;69(6):1012–20.
82. Kayaselçuk F, Demirhan B, Kayaselçuk U, Ozerdem OR, Tuncer I. Vimentin, SMA, desmin, S-100 protein, p53, and estrogen receptor expression in elastofibroma and nodular fasciitis. Ann Diagn Pathol. 2002;6(2):94–9.
83. Kazakov DV, Kyrpychova L, Martinek P, Grossmann P, Steiner P, Vanecek T, Pavlovsky M, Bencik V, Michal M, Michal M. ALK gene fusions in epithelioid fibrous histiocytoma: a study of 14 cases, with new histopathologic findings. Am J Dermatopathol. 2018. https://doi.org/10.1097/DAD.0000000000001085.
84. Keasbey LE. Juvenile aponeurotic fibroma (calcifying fibroma); a distinctive tumor arising in the palms and soles of young children. Cancer. 1953;6(2):338–46.
85. Kitano Y. Juvenile hyalin fibromatosis. Arch Dermatol. 1976;112(1):86–8.
86. Kucher C, McNiff JM. Epithelial fibrous papule-a new variant. J Cutan Pathol. 2007;34:571–5.
87. Kumar E, Patel NR, Demicco EG, Bovee JV, Olivera AM, Lopez-Terrada DH, Billings SD, Lazar AJ, Wang WL. Cutaneous nodular fasciitis with genetic analysis: a case series. J Cutan Pathol. 2016;43(12):1143–9.
88. Kuo TT, Hu S, Chan HL. Keloidal dermatofibroma: report of 10 cases of a new variant. Am J Surg Pathol. 1998;22(5):564–8.
89. Kuo TT, Chen TC, Lee LY. Sclerosing angiomatoid nodular transformation of the spleen (SANT): clinicopathological study of 10 cases with or without abdominal disseminated calcifying fibrous tumors, and the presence of a significant number of IgG4+ plasma cells. Pathol Int. 2009;59(12):844–50.
90. Kutzner H, Mentzel T, Palmedo G, Hantschke M, Rütten A, Paredes BE, Schärer L, Guillen CS, Requena L. Plaque-like CD34 positive dermal fibroma ("medallion-like dermal dendrocyte hamartoma"): clinicopathologic, immunohistochemical, and molecular analysis of 5 cases emphasizing its distinction from superficial, plaque-like dermatofibrosarcoma protuberans. Am J Surg Pathol. 2010;34(2):190–201.
91. Lambert CM, Nuki G. Multicentric reticulohistiocytosis with arthritis and cardiac infiltration: regression following treatment for underlying malignancy. Ann Rheum Dis [Case Reports]. 1992;51(6):815–7.
92. Lamovec J, Bracko M, Voncina D. Pleomorphic fibroma of tendon sheath. Am J Surg Pathol. 1991;15:1202–5.
93. Laskin WB, Miettinen M, Fetsch JF. Infantile digital fibroma/fibromatosis: a clinicopathologic and immunohistochemical study of 69 tumors from 57 patients with long-term follow-up. Am J Surg Pathol. 2009;33(1):1–13.
94. Lauer DH, Enzinger FM. Cranial fasciitis of childhood. Cancer. 1980;45(2):401–6.
95. Lehmer LM, Moore JB, Ragsdale BD. Ischemic fasciitis: enhanced diagnostic resolution through clinical, histopathologic and radiologic correlation in 17 cases. J Cutan Pathol. 2016;43(9):740–8.
96. Liegl B, Fletcher CD. Ischemic fasciitis: analysis of 44 cases indicating an inconsistent association with immobility or debilitation. Am J Surg Pathol. 2008;32(10):1546–52.
97. Linos K, Sedivcová M, Cerna K, Sima R, Kazakov DV, Nazeer T, et al. Extra nuchal-type fibroma associated with elastosis, traumatic neuroma, a rare APC gene missense mutation, and a very rare MUTYH gene polymorphism: a case report and review of the literature. J Cutan Pathol. 2011;38(11):911–8. PMID:21752055.
98. Macchia G, Trombetta D, Möller E, Mertens F, Storlazzi CT, Debeiec-Rychter M, Sciot R, Nord KH. FOSL1 as a candidate target gene for 11q12 rearrangements in desmoplastic fibroblastoma. Lab Investig. 2012;92(5):735–43.
99. Maeda A, Kawabata K, Kusuzaki K. Rapid recurrence of calcifying fibrous pseudotumor (a case report). Anticancer Res. 2002;22(3):1795–7.
100. Magro G, Michal M, Alaggio R, et al. Intradermal proliferative fasciitis in childhood: a potential diagnostic pitfall. J Cutan Pathol. 2011;38(1):59–62.
101. Marcoval J, Moreno A, Bordas X, et al. Diffuse plane xanthoma: clinicopathologic study of 8 cases. J Am Acad Dermatol. 1998;39(3):439–42.
102. Marino-Enriquez A, Fletcher CD. Angiofibroma of soft tissue: clinicopathologic characterization of a distinctive benign fibrovascular neoplasm in a series of 37 cases. Am J Surg Pathol. 2012;36(4):500–8.
103. Marque M, Bessis D, Pedeutour F, Viseux V, Guillot B, Fraitag-Spinner S. Medallion-like dermal dendrocyte hamartoma: the main diagnostic pitfall is congenital atrophic dermatofibrosarcoma. Br J Dermatol. 2009;160(1):190–3.
104. McNiff JM, Subtil A, Cowper SE, Lazova R, Glusac EJ. Cellular digital fibromas: distinctive CD34-positive lesions that may mimic dermatofibrosarcoma protuberans. J Cutan Pathol. 2005;32(6):413–8.

105. Mehrad M, LaFramboise WA, Lyons MA, Trejo Bittar HE, Yousem SA. Whole exome sequencing identifies unique mutations and copy number losses in calcifying fibrous tumor of the pleura: report of three cases and review of the literature. Hum Pathol. 2018. pii: S0046-8177(18)30125–4. https://doi.org/10.1016/j.humpath.2018.04.005. [Epub ahead of print].
106. Meis JM, Enzinger FM. Proliferative fasciitis and myositis of childhood. Am J Surg Pathol. 1992;16(4):364–72.
107. Mentzel T, Kutzner H. Dermatomyofibroma: clinicopathologic and immunohistochemical analysis of 56 cases and reappraisal of a rare and distinct cutaneous neoplasm. Am J Dermatopathol. 2009;31:44.
108. Mentzel T, Kutzner H, Rütten A, Hügel H. Benign fibrous histiocytoma (dermatofibroma) of the face: clinicopathologic and immunohistochemical study of 34 cases associated with an aggressive clinical course. Am J Dermatopathol. 2001;23(5):419–26.
109. Mentzel T, Wiesner T, Cerroni L, Hantschke M, Kutzner H, Rütten A, et al. Malignant dermatofibroma: clinicopathological, immunohistochemical, and molecular analysis of seven cases. Mod Pathol. 2013;26(2):256–67.
110. Metcalf JS, Maize JC, LeBoit PE. Circumscribed storiform collagenoma (sclerosing fibroma). Am J Dermatopathol. 1991;13(2):122–9.
111. Michael M, Fetsch JF, Hes O, Miettinen M. Nuchal-type fibroma: A clinical pathologic study 52 cases. Cancer. 1999;85(1):156–63.
112. Michal M, Mukensnabl P, Chlumska A, et al. Fibrous hamartoma of infancy. A study of eight cases with immunohistochemical and electron microscopical findings. Pathol Res Pract. 1992;188:1049–53.
113. Miettinen M, Fetch JF. Collagenous fibroma (desmoplastic fibroblastoma): A clinicopathologic analysis of 63 cases of a distinctive soft tissue lesion with stellate-shaped fibroblasts. Hum Pathol. 1998;29:676–82.
114. Miettinen M, Fetsch JF. Reticulohistiocytoma (solitary epithelioid histiocytoma): a clinicopathologic and immunohistochemical study of 44 cases. Am J Surg Pathol. 2006;30(4):521–8.
115. Monaghan H, Salter DM, Al-Nafussi A. Giant cell tumour of tendon sheath (localised nodular tenosynovitis): clinicopathological features of 71 cases. J Clin Pathol. 2001;54(5):404–7.
116. Montgomery EA, Meis JM. Nodular fasciitis. Its morphologic spectrum and immunohistochemical profile. Am J Surg Pathol. 1991;15(10):942–8.
117. Montgomery H, Osterberg AE. Xanthomatosis: correlation of clinical histopathologic and chemical studies of cutaneous xanthoma. Arch Dermatol Syph. 1938;37:373.
118. Montgomery E, Lee JH, Abraham SC, Wu TT. Superficial fibromatoses are genetically distinct from deep fibromatoses. Mod Pathol. 2001;14(7):695–701. PMID:11455002.
119. Moosavi CA, Al-Nahar LA, Murphey MD, Fanburg-Smith JC. Fibroosseous pseudotumor of the digit: a clinicopathologic study of 43 new cases. Ann Diagn Pathol. 2008;12(1):21–8.
120. Nagamine N, Nohara Y, Ito E. Elastofibroma in Okinawa. A clinicopathologic study of 170 cases. Cancer. 1982;50(9):1794–805.
121. Nascimento AG. A clinicopathologic and immunohistochemical comparative study of cutaneous and intramuscular forms of juvenile xanthogranuloma. Am J Surg Pathol. 1997;21(6):645–52.
122. Nofal A, Sanad M, Assaf M, et al. Juvenile hyaline fibromatosis and infantile systemic hyalinosis: a unifying term and a proposed grading system. J Am Acad Dermatol. 2009;61(4):695–700.
123. Page RN, King R, Mihm MC Jr, Googe PB. Microphthalmia transcription factor and NKI/C3 expression in cellular neurothekeoma. Mod Pathol. 2004;17:230–4.
124. Patchefsky AS, Enzinger FM. Intravascular fasciitis: a report of 17 cases. Am J Surg Pathol. 1981;5(1):29–36.
125. Paties C, Vassallo G, Taccagni GL. Clear cell dermatofibroma. Am J Surg Pathol. 1997;21(2):250–2.
126. Paxton CN, O'Malley DP, Bellizzi AM, Alkapalan D, Fedoriw Y, Hornick JL, Perkins SL, South ST, Andersen EF. Genetic evaluation of juvenile xanthogranuloma: genomic abnormalities are uncommon in solitary lesions, advanced cases may show more complexity. Mod Pathol. 2017;30(9):1234–40.
127. Pennacchia I, Kutzner H, Kazakov DV, Mentzel T. Fibroblastic connective tissue nevus: clinicopathological and immunohistochemical study of 14 cases. J Cutan Pathol. 2017;44(10):827–34.
128. Pérez LP, Zulaica A, Rodríguez L, Campo MC, Peñaranda JM, Fernández-Redondo V, et al. Multinucleate cell angiohistiocytoma. Report of five cases. J Cutan Pathol. 2006;33:349–52.
129. Perosio PM, Weiss SW. Ischemic fasciitis: a juxtaskeletal fibroblastic proliferation with a predilection for elderly patients. Mod Pathol. 1993;6(1):69–72.
130. Pezhouh MK, Rezaei MK, Shabihkhani M, Ghosh A, Belchis D, Montgomery EA, Voltaggio L. Clinicopathologic study of calcifying fibrous tumor of the gastrointestinal tract: a case series. Hum Pathol. 2017;62:199–205.
131. Pulitzer DR, Martin PC, Reed RJ. Fibroma of tendon sheath. A clinicopathologic study of 32 cases. Am J Surg Pathol. 1989;13(6):472–9.
132. Puls F, Hofvander J, Magnusson L, Nilsson J, Haywood E, Sumathi VP, et al. FN1-EGF gene fusions are recurrent in calcifying aponeurotic fibroma. J Pathol. 2016;238(4):502–7. PMID:26691015.
133. Rao AS, Vigorita VJ. Pigmented villonodular synovitis (giant-cell tumor of the tendon sheath and synovial membrane). A review of eighty-one cases. J Bone Joint Surg Am. 1984;66(1):76–94.
134. Rapini RP, Golitz LE. Sclerotic fibromas of the skin. J Am Acad Dermatol. 1989;20(2 Pt 1):266–271. PMID:2464630.
135. Ravić-Nikolić A, Mladenović V, Mitrović S, Miličić V, Djukić A, Jovović-Dagović B, Savčić G. Generalized

eruptive xanthomas associated with diabetic dyslipidemia. Eur J Dermatol. 2014;24(3):394–5.
136. Requena L, Gutiérrez J, Sánchez Yus E. Multiple sclerotic fibromas of the skin. A cutaneous marker of Cowden's disease. J Cutan Pathol. 1992;19(4):346–351. PMID:1430474.
137. Reye RD. Recurring digital fibrous tumors of childhood. Arch Pathol. 1965;80:228–31.
138. Rosa G, Billings SD. A report of three cases of pediatric proliferative fasciitis. J Cutan Pathol. 2014;41(9):720–3.
139. Rougemont AL, Fetni R, Murthy S, et al. A complex translocation (6;12;8)(q25;q24.3;q13) in a fibrous hamartoma of infancy. Cancer Genet Cytogenet. 2006;171:115–8.
140. Saab ST, McClain CM, Coffin CM. Fibrous hamartoma of infancy: a clinicopathologic analysis of 60 cases. Am J Surg Pathol. 2014;38(3):394–401.
141. Sachak T, Heerema NA, Mayerson J, Payne JE, Parwani A, Iwenofu OH. Novel t(1;2)(p36.1;q23) and t(7;19)(q32;q13.3) chromosomal translocations in ischemic fasciitis: expanding the spectrum of pseudosarcomatous lesions with clonal pathogenetic link. Diagn Pathol. 2018;13(1):18.
142. Schaffer JV, Gohara MA, McNiff JM, et al. Multiple facial angiofibromas: A cutaneous manifestation of Birt–Hogg–Dubé syndrome. J Am Acad Dermatol. 2005;53:S108–11.
143. Sciot R, Samson I, van den Berghe H, van Damme B, Dal CP. Collagenous fibroma (desmoplastic fibroblastoma): Genetic link with fibroma of tendon sheath? Mod Pathol. 1999a;12:565–8.
144. Sciot R, Rosai J, Dal Cin P, et al. Analysis of 35 cases of localized and diffuse tenosynovial giant cell tumor: a report from the Chromosomes and Morphology (CHAMP) study group. Mod Pathol. 1999b;12(6):576–9.
145. Shek TW, Chan AC, Ma L. Extra-nuchal nuchal fibroma. Am J Surg Pathol. 1996;20(7):902–3.
146. Shimizu S, Hashimoto H, Enjoji M. Nodular fasciitis: an analysis of 250 patients. Pathology. 1984;16(2):161–6.
147. Sigel JE, Smith TA, Reith JD, et al. Immunohistochemical analysis of anaplastic lymphoma kinase expression in deep soft tissue calcifying fibrous pseudotumor: evidence of a late sclerosing stage of inflammatory myofibroblastic tumor? Ann Diagn Pathol. 2001;5(1):10–4.
148. Singh Gomez C, Calonje E, Fletcher CD. Epithelioid benign fibrous histiocytoma of skin: clinicopathological analysis of 20 cases of a poorly known variant. Histopathology. 1994;24(2):123–9.
149. Smith NP, Wilson JE. Multinucleate cell angiohistiocytoma: a new entity. Br J Dermatol. 1985; 113:15.
150. Somerhausen NS, Fletcher CD. Diffuse-type giant cell tumor: clinicopathologic and immunohistochemical analysis of 50 cases with extraarticular disease. Am J Surg Pathol. 2000;24(4):479–92.
151. Soyer HP, Kutzner H, Metze D, et al. Clear-cell fibrous papule. J Cutan Pathol. 1996;23:62.
152. Stratton J, Billings SD. Cellular neurothekeoma: analysis of 37 cases emphasizing atypical histologic features. Mod Pathol. 2014;27:701–10.
153. Stuart LN, Hiatt KM, Zohreh Z, Gardner JM, Shalin SC. Plaque-like CD34-positive dermal fibroma/medallion-like dendrocyte hamartoma: an unusual spindle cell neoplasm. J Cutan Pathol. 2014;41:625–9.
154. Tamada S, Ackerman AB. Dermatofibroma with monster cells. Am J Dermatopathol. 1987;9(5):380–7. PMID:2825558.
155. Tardío JC, Butrón M, Martín-Fragueiro LM. Superficial acral fibromyxoma: report of 4 cases with CD10 expression and lipomatous component, two previously under recognized features. Am J Dermatopathol. 2008;30(5):431–5.
156. Tashakori M, Pimentl J, Howitt BE, Sanchez J, Michalowski S, Chitale D, Ormsby AH, Williamson SR. Pleomorphic fibroma of the skin with MDM2 immunoreactivity: A potential diagnostic pitfall. J Cutan Pathol. 2018;45(1):59–62.
157. Techavichit P, Sosothikul D, Chaichana T, Teerapakpinyo C, Thorner PS, Shuangshoti S. BRAF V600E mutation in pediatric intracranial and cranial juvenile xanthogranuloma. Hum Pathol. 2017;69:118–22.
158. Tran P, McLemore M. Atypical cellular neurothekeoma: a potential diagnostic pitfall for benign and malignant spindle cell lesions in skin. J Cutan Pathol. 2018. https://doi.org/10.1111/cup.13274. [Epub ahead of print].
159. Tran TA, Hayner-Buchan A, Jones DM, McRorie D, Carlson JA. Cutaneous balloon cell dermatofibroma (fibrous histiocytoma). Am J Dermatopathol. 2007;29(2):197–200.
160. Ushijima M, Tsuneyoshi M, Enjoji M. Dupuytren type fibromatoses. A clinicopathologic study of 62 cases. Acta Pathol Jpn. 1984;34(5):991–1001. PMID:6507097.
161. Ushijima M, Hashimoto H, Tsuneyoshi M, et al. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. Cancer. 1986;57(4):875–84.
162. Val-Bernal JF, Mira C. Dermatofibroma with granular cells. J Cutan Pathol. 1996;23(6):562–5. PMID:9001988.
163. Van Dorpe J, Ectors N, Geboes K, et al. Is calcifying fibrous pseudotumor a late sclerosing stage of inflammatory myofibroblastic tumor? Am J Surg Pathol. 1999;23(3):329–35.
164. Vanni R, Fletcher CD, Sciot R, Dal Cin P, De Wever I, Mandahl N, et al. Cytogenetic evidence of clonality in cutaneous benign fibrous histiocytomas: a report of the CHAMP study group. Histopathology. 2000;37(3):212–7. PMID:10971696.
165. Veugelers M, Wilkes D, Burton K, McDermott DA, Song Y, Goldstein MM, et al. Comparative PRKAR1A genotype-phenotype analyses in humans with Carney complex and prkar1a haploinsufficient mice. Proc Natl Acad Sci U S A. 2004;101(39):14222–7.

166. Walther C, Hofvander J, Nilsson J, Magnusson L, Domanski HA, Gisselsson D, et al. Gene fusion detection in formalin-fixed paraffin-embedded benign fibrous histiocytomas using fluorescence in situ hybridization and RNA sequencing. Lab Investig. 2015;95(9):1071–6. PMID:26121314.
167. Wambacher-Gasser B, Zelger B, Zelger BG, Steiner H. Clear cell dermatofibroma. Histopathology. 1997;30(1):64–9. PMID:9023559.
168. Wang GY, Nazarian RM, Zhao L, Hristov AC, Patel RM, Fullen DR, Chan MP. Protein gene product 9.5 (PGP9.5) expression in benign cutaneous mesenchymal, histiocytic, and melanocytic lesions: comparison with cellular neurothekeoma. Pathology. 2017;49(1):44–9.
169. Wehrli BM, Weiss SW, Yandow S, Coffin CM. Gardner associated fibromas (GAF) in young patients: A distinct fibrous lesion that identifies unsuspected Gardner's syndrome and risk for fibromatosis. Am J Surg Pathol. 2001;25(5):645–51.
170. Weinreb I, Shaw AJ, Perez-Ordoñez B, et al. Nodular fasciitis of the head and neck region: a clinicopathologic description in a series of 30 cases. J Cutan Pathol. 2009;36(11):1168–73.
171. West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci U S A. 2006;103(3):690–5.
172. Winkelmann RK. Cutaneous syndromes of non-X histiocytosis. A review of the macrophage-histiocyte diseases of the skin. Arch Dermatol. 1981;117(10):667–72.
173. Yamada Y, Yamamoto H, Kohashi K, Ishii T, Iura K, Maekawa A, Bekki H, Otsuka H, Yamashita K, Tanaka H, Hiraki T, Mukai M, Shirakawa A, Shinnou Y, Jinno M, Yanai H, Taguchi K, Maehara Y, Iwamoto Y, Oda Y. Histological spectrum of angiofibroma of soft tissue: histological and genetic analysis of 13 cases. Histopathology. 2016;69(3):459–69.
174. Yamawaki S, Naitoh M, Kubota H, Aya R, Katayama Y, Ishiko T, Tamura T, Yoshikawa K, Enoshiri T, Ikeda M, Suzuki S. Htra1 is specifically up-regulated in active keloid lesions and stimulates keloid development. Int J Mol Sci. 2018;19(5):pii: E1275.
175. Yantiss RK, Nielsen GP, Lauwers GY, et al. Reactive nodular fibrous pseudotumor of the gastrointestinal tract and mesentery: a clinicopathologic study of five cases. Am J Surg Pathol. 2003;27(4):532–40.
176. Zelger B, Cerio R, Soyer HP, et al. Reticulohistiocytoma and multicentric reticulohistiocytosis. Histopathologic and immunophenotypic distinct entities. Am J Dermatopathol [Comparative Study]. 1994;16(6):577–84.
177. Zelger BW, Zelger BG, Steiner H, Ofner D. Aneurysmal and haemangiopericytoma-like fibrous histiocytoma. J Clin Pathol. 1996;49(4):313–8.