**MULTINUCLEATE CELL ANGIOHISTIOCYTOMA**

**Definition**
A distinctive benign dermal proliferation composed of thin-walled capillaries and veins, admixed with scattered multinucleated cells.

**Clinical Features**

- **Epidemiology**
  - Female predominance (F:M = 3:1)
  - Middle-aged adult patients

- **Presentation**
  - Slowly growing single or multiple firm, red-brown to violaceous papules
  - Multiple lesions usually distributed over the same area, occasionally bilateral
  - Surface is usually smooth, occasionally scaly
  - Size less than 1 cm in diameter
  - Most common over distal extremities, particularly dorsum of hands, wrists, thighs, and legs, with less frequent involvement of the face and trunk
  - Mucosal sites distinctly uncommon (oral cavity)
  - Usually asymptomatic, pruritic lesions rare
  - Clinical variants
    - Linear
    - Eruptive
    - Plaquelike
    - Disseminated/generalized

- **Prognosis and Treatment**
  - Spontaneous regression possible, but rare
  - Association with mycosis fungoides, diabetes mellitus, or vitiligo most likely coincidental

**Pathology**

- **Histology**
  - Vascular proliferation, composed predominantly of thin-walled capillaries and veins
  - Lumina dilated or narrow
  - Lined by a single layer of bland endothelial cells
  - Each vessel surrounded by layer of pericytes
  - Scattered multinucleated cells
  - Bizarre shaped
  - Hyperchromatic nuclei
  - Angulated cytoplasm

- Fibroblast-like and histiocyte-like mononuclear cells
- Thickened collagen bundles, frequently hyalinized
- Occasional inflammatory cells, predominantly lymphocytes
- Hemorrhage absent, no hemosiderin deposition
- Decreased elastic fibers in the dermis can be observed
- Overlying epidermis normal, but can also be hyperplastic
- Proliferation restricted to upper and middermis

**Immunopathology/Special Stains**
- Multinucleated cells display variable CD68 positivity
- Vascular markers delineate endothelial cells

**Main Differential Diagnoses**
- Atrophic dermatofibroma
- Microvascular hemangioma
- Angiofibroma
- Kaposi sarcoma

**Fig. 1.** Multinucleate cell angiohistiocytoma. Acral skin with a slight increase in the number of blood vessels, mild dermal fibrosis, and scattered multinucleated giant cells. Note also mild perivascular inflammatory cell infiltrate.
Fig. 2. Multinucleate cell angiohistiocytoma. Another area featuring distinctive multinucleated giant cells in the dermis, proliferation of small blood vessels, mild fibrosis, and perivascular inflammation.

Fig. 3. Multinucleate cell angiohistiocytoma—higher magnification.
BENIGN FIBROUS HISTIOCYTOMA
(DERMATOFIBROMA)

**Definition**
- One of the most common benign soft tissue proliferations in the skin
- Neoplastic process is favored over a reactive condition due to the absence of spontaneous regression, tendency for local recurrence(s), extremely rare locoregional and distant metastases, as well as the recent detection of fusions in protein kinase C and membrane-associated proteins in some fibrous histiocytes
- Represents a group of morphologically diverse proliferations with different clinical presentations and biological potential

**Clinical features**

**Epidemiology**
- Broad age distribution, most common in middle-aged adults
- Slight female predominance

**Presentation**
- Virtually any site of skin can be affected
- Most commonly on the limbs (about 70%), followed by the trunk
- Slowly growing, firm solitary nodule, round to oval
- Overlying skin often reddish-brown to darkly pigmented and scaly
- Size of the lesion is usually less than 10 mm
- Central dimple formation on lateral compression or squeezing is a common clinical sign
- History of previous trauma occasionally present
- Clinical variants
  - Giant variant, including plaquelike, measuring from 35 to 300 mm
  - Eruptive variant, usually related to immunosuppression, HIV infection, and highly active antiretroviral therapy

**Prognosis and treatment**
- Simple excision is curative
- Recurrences after incomplete or marginal excision have been estimated to develop in less than 2% of cases
- Lesions occurring on the face and certain morphological variants (cellular, aneurysmal, atypical) are associated with a higher recurrence rate (up to 26%)
- Rare metastases have been reported in particular variants of fibrous histiocytoma (cellular, aneurysmal, atypical); however, no histological features have been detected to predict metastatic potential

**Pathology**

**Histology**
- Epidermis above the lesion is usually hyperplastic
- Elongation and broadening of rete ridges associated with hyperpigmentation of basal keratinocytes especially over the tips of rete ridges (so-called dirty fingers)
  - Proliferation of immature hair-follicle structures above the dermal proliferation is frequently seen and can mimic a basal cell carcinoma or an adnexal tumor
  - Papillary dermis is usually, but not always, spared (so-called grenz zone)
  - Defining histological features include
    - Spindle cells growing in a haphazard, vague, storiform or short intersecting fascicular pattern
    - Histiocytes in variable proportions, including multinucleated giant cells (routon and foreign body type), siderophages, and foamy cells
    - Inflammatory cells in variable proportions, usually lymphocytes
    - Delicate collagenous or loosely myxoid stroma containing thin-walled blood vessels
    - Ill-defined nonencapsulated proliferation in the dermis/superficial subcutis
    - Growth into subcutis usually in the form of short extensions
    - Individual bundles of collagen surrounding by lesional cells, so-called collagen trapping, especially at the periphery of the lesion
  - Lesions restricted to subcutis or deeper structures rare
  - Several histological variants have been recognized, including cellular, epithelioid, aneurysmal, atypical (pseudosarcomatoid), lipidized (ankle type), clear cell, palisading, deep, signet sing cell, fibrous histiocytoma with osteoclast-like cells, cholesterotic
  - Different variants can coexist within a single lesion

**Immunopathology/special stains**
- Although factor XIIIa is usually positive, it may just delineate a background population of dermal dendrocytes
- See variants for additional immunohistochemical features

**Molecular genetic features**
- Gene fusions involving multiple protein kinase C-encoding genes (PRKCA, PRKCB, or PRKCD) with a variety of other genes have been documented
- The prevalence and distribution of these fusions in the various subtypes of benign fibrous histiocytoma are not known, but they are only present in a subset.

**Main differential diagnoses**
- Nodular fasciitis
- Dermatofibrosarcoma protuberans
- Scar
- Xanthoma
- Xanthogranuloma
- Melanocytic lesions

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Benign Fibrous Histiocytoma (Dermatofibroma)

Fig. 1. Benign fibrous histiocytoma—dermatofibroma. Classic appearance of an ill-defined dermal tumor associated with overlying epidermal hyperplasia.

Fig. 2. Benign fibrous histiocytoma—dermatofibroma. Variably cellular, polymorphic dermal tumor that can involve the full thickness of the dermis.

Fig. 3. Benign fibrous histiocytoma—dermatofibroma. Focal involvement of the subcutis is relatively common.

Fig. 4. Benign fibrous histiocytoma—dermatofibroma. The tumor is generally composed of an admixture of spindle cells and histiocyte-like cells, albeit in variable proportions.
Fig. 5. Benign fibrous histiocytoma—dermatofibroma. High-power view of spindle-shaped tumor cells displaying a storiform growth pattern.

Fig. 6. Benign fibrous histiocytoma—dermatofibroma. In this example, spindle cells in a curlicue and focal storiform growth pattern are embedded in collagenous hyalinized stroma.

Fig. 7. Benign fibrous histiocytoma—dermatofibroma, higher magnification. An admixture of spindle and histiocyte-like cells is noted. Note also the presence of an inflammatory cell infiltrate composed of lymphocytes.

Fig. 8. Benign fibrous histiocytoma—dermatofibroma. Occasional normal mitoses are not uncommon. In addition, note the prominent deposition of hemosiderin in this example.

Fig. 9. Benign fibrous histiocytoma—dermatofibroma. Collagen trapping is typically present at the periphery of the tumor. This is an important clue as an aid in recognizing the entity.

Fig. 10. Benign fibrous histiocytoma—dermatofibroma. The epidermis overlying dermatofibroma is frequently acanthotic. A grenz zone separates the tumor from the epidermis.
Fig. 11. Benign fibrous histiocytoma—dermatofibroma. Elongation and broadening of the rete ridges associated with hyperpigmentation of basal keratinocytes in the epidermis overlying the tumor.

Fig. 12. Benign fibrous histiocytoma—dermatofibroma. Proliferation of immature hair follicle structures reminiscent of trichoblastoma is not uncommonly seen above the dermal proliferation and should not be mistaken for basal cell carcinoma.

Fig. 13. Benign fibrous histiocytoma—dermatofibroma. Trichoblastoma-like basaloid proliferation, high-power magnification.

Fig. 14. Benign fibrous histiocytoma—dermatofibroma. Prominent hemosiderin deposition is typical of the hemosiderotic variant. Note the presence of multinucleated giant cells.
CELLULAR FIBROUS HISTIOCYTOMA

s0170 Definition

p0785 • Distinctive variant of a benign fibrous histiocytoma (dermatofibroma), characterized by highly cellular monomorphic proliferation of spindle cells growing in a more fascicular and focally storiform pattern

s0175 Clinical features

s0180 Epidemiology

p0795 • Represents about 5% of benign fibrous histiocytomas

u0685 • Approximately equal gender distribution, although slight male predominance observed in the initial publication

u0690 • Wide age distribution, but most common in young to middle-aged adults (between 33 and 42 years)

s0185 Presentation

p0815 • Solitary asymptomatic nodule

u0700 • Multifocal growth and familial occurrence in a single patient

u0705 • Preoperative duration of the lesion variable (2 weeks–2 years)

u0710 • Upper limb/limb girdle followed by lower limb/limb girdle, head and neck, and trunk

u0715 • Propensity for unusual sites, like face, ears, hands, and feet

s0190 Prognosis and treatment

p0845 • Complete excision usually curative

u0725 • Recurrence rate as high as 26% after incomplete/marginal excision

u0730 • Locoregional (lymph nodes) and systemic metastases (lungs) in exceptional cases; no histological features have been detected to predict metastatic potential

s0195 Pathology

s0200 Histology

p0865 • Two growth patterns recognized on low-power examination

u0740 • Nonexophytic and ill defined (more common)

u0745 • Exophytic and circumscribed

u0750 • Defining features include

u0755 • Cellular proliferation of plump spindle cells with tapering nuclei containing small eosinophilic nucleoli and relatively abundant ill-defined, pale eosinophilic cytoplasm

u0760 • Short fascicular growth predominates over storiform growth pattern

u0765 • Foci of more epithelioid cells occasionally present and represent a minor component of the lesion

u0770 • Normal mitoses common (up to 10 mitoses per 10 high-power fields)

u0775 • Abnormal mitoses not present

u0780 • Focal necrosis (in up to 12%), generally not associated with surface ulceration

u0785 • Surface ulceration uncommon

u0790 • Most frequently arise in superficial dermis and subsequently infiltrate the deep dermis, but middermal and deep dermal origin not uncommon

• Extension into the subcutis present in roughly one-third of the cases

• Fascicular growth along the septa (perpendicular to the epidermis)

• Lacelike growth between the fat cells

• Infiltration beyond subcutis into the underlying skeletal muscle rare, usually in the head and neck area, most likely due to the more superficial localization of skeletal muscles at this particular site

• Areas of a classical benign fibrous histiocytoma consistently identified at least focally, usually at the periphery of the cellular proliferation

Immunopathology/special stains

• Smooth muscle actin (SMA) positivity in over 90%

• Cytoplasmic desmin positivity in 32%

• Consistent with myofibroblastic differentiation

• Genuine CD34 positivity in 6%

• Usually seen at the periphery of the lesion or in a patchy pattern

• Diffuse CD34 staining is an exception

• Consistently negative for cytokeratins, S100 protein, and EMA

• Factor XIIIa reveals nonneoplastic cells in the background

Main differential diagnoses

• Atypical dermal smooth muscle tumor

• Dermatofibrosarcoma protuberans

Fig. 1. Cellular fibrous histiocytoma. Note an ill-defined, highly cellular dermal tumor. Extension into subcutis is present in about one-third of the cases, mainly along the fibrous septa.
Fig. 2. Cellular fibrous histiocytoma. This example shows extensive infiltration of the subcutis.

Fig. 3. Cellular fibrous histiocytoma. Highly cellular proliferation of monomorphic fascicles of myofibroblast-like spindle cells associated with lymphocytes in the background.

Fig. 4. Cellular fibrous histiocytoma. Note a more polymorphic area containing spindle-shaped cells, histiocyte-like cells, and lymphocytes.
Fibrohistiocytic Tumors

Fig. 5. Cellular fibrous histiocytoma—higher magnification. Bland spindle cells growing in short fascicles. Note focal storiform growth pattern.

Fig. 6. Cellular fibrous histiocytoma. Areas of necrosis are present in about 10% of the tumors and have no prognostic implication.

Fig. 7. Cellular fibrous histiocytoma. Mitotic activity can be brisk. Atypical mitoses are generally absent.
Cellular Fibrous Histiocytoma

Fig. 8. Cellular fibrous histiocytoma. This example displays scattered large atypical cells indicating a tumor combining features of cellular and atypical fibrous histiocytoma.

Fig. 9. Cellular fibrous histiocytoma. This example is characterized by granular cell change.

Fig. 10. Cellular fibrous histiocytoma. A rare finding of pseudo-vascular invasion shows tumor cells protruding into the lumen of a small vein.

Fig. 11. Cellular fibrous histiocytoma—CD34 immunohistochemistry. Patchy positivity can frequently be observed at the periphery of the tumor. Focal positivity of tumor cells for this marker can be seen in other areas of the tumor, but diffuse positivity as seen in dermatofibrosarcoma protuberans is not usually a feature.
ANEURYSMAL FIBROUS HISTIOCYTOMA

**Definition**
Distinctive variant of a benign fibrous histiocytoma (dermatofibroma), characterized by formation of variably sized, blood-filled spaces developing in the background of an ordinary common benign fibrous histiocytoma.

**Clinical features**

**Epidemiology**
- Represents less than 2% of fibrous histiocytomas
- Develops most frequently in the fourth decade of life (mean age 37 years)
- Shows female predominance, with male-to-female ratio of 1:1.5

**Presentation**
- Broad anatomical distribution with predilection for the lower limbs/limb girdle (55%), followed by upper limbs/limb girdle (17%), trunk (12%), and head and neck (4%)
- Solitary papule of variegated color from dark brown to red or blue
- Diameter of the lesion from 5 to 40 mm
- Multiple lesions develop exceptionally
- Rapid growth due to hemorrhage within the preexistent long-standing lesion is a common presenting symptom

**Prognosis and treatment**
- Simple excision is usually curative
- Recurrences after incomplete/marginal excision are common (up to 20%)
- Metastatic disease exceptional, no histological features have been detected to predict metastatic potential

**Pathology**

**Histology**
- Epidermis overlying the lesion demonstrates variable degrees of acanthosis
- Generally located in the dermis, extension into the subcutis not uncommon, but infiltration into the underlying skeletal muscle rare
- The lesion can be ill defined
- Defining features include blood-filled spaces ranging from slitlike to large cavities, similar to cavernous hemangioma
- Blood-filled spaces
  - Lack of endothelial lining
  - Are lined by the lesional cells, including histiocytes, fibroblasts, and giant cells
  - Are most frequently located within the most cellular parts of the lesion, usually central, which are devoid of collagen and elastic fibers
  - Can represent the predominant component of the lesion
- Surrounding stroma contains numerous small capillaries, prominent interstitial hemorrhage, and hemosiderin deposition
- Classical histological features of benign fibrous histiocytoma can usually be recognized at the periphery of the lesion

**Immunopathology/special stains/cytogenetics**
- Lesional cells can stain focally for smooth muscle actin
- Factor XIIIa– and CD34-positive cells may represent reactive cells within the lesion
- Lesional cells are consistently negative for desmin, CD34, CD31, CD68, and factor XIIIa
- t(12;19)(p12;q13) detected in a single case

**Main differential diagnoses**
- Angiomatoid fibrous histiocytoma
- Spindle cell hemangioma
- Nodular Kaposi sarcoma
- Angiosarcoma

**Fig. 1.** Aneurysmal fibrous histiocytoma. Tumor with variably sized, blood-filled spaces mimicking blood vessels in the background of an ordinary fibrous histiocytoma.

**Fig. 2.** Aneurysmal fibrous histiocytoma. Note numerous pseudovascular spaces with prominent hemorrhage and artifactual slitlike spaces.