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Dermatofibroma—A Critical Evaluation

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Dermatofibromas are common cutaneous lesions. In most cases, they can be readily identified clinically and show a typical histology. In a small percentage of cases they show unusual clinical and more often histologic features that may cause differential diagnostic problems. In addition there are reactive fibrous lesions with neural or smooth muscle features that we speculate may represent dermatofibroma variants.
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Dermatofibromas (DF) are generally regarded as rather uninteresting lesions. They are extremely common but burdened by a long list of hopeless synonyms that discourage all but the most intrepid student. In addition, they are almost always banal, asymptomatic, and often better left untreated. There is little agreement on their true nature—is a DF a neoplasm/tumor or a reactive process? What is the cell of origin—a histiocyte, a macrophage, a fibroblast, a myofibroblast? How can one unequivocally identify a DF, or what special stains really help?

We find DF to be a fascinating lesion, worthy of attention. We will try to answer these questions, discuss the wide variety of both clinical and histologic variants of DF, and review its clinical associations. In addition, a number of lesions we feel share many features with DF although they are considered to be smooth muscle or neural tumors. We would like to provocatively suggest that some of these tumors may also be DF variants.

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Definition

What is a DF? We suggest the following:

DF is a fibrosing dermatitis characterized by an increased number of fibrocytes in the dermis and occasionally subcutis; a variable admixture of macrophages and other inflammatory cells including frequently lymphocytes, rarely eosinophils, neutrophils, and/or plasma cells, with coarse collagen bundles in haphazard array often with peripheral entrapment; as well as hyperplasia of adjacent structures (epidermis, hair follicles) or cells (melanocytes).

Not surprisingly this definition shares many features with the official definition in the new WHO classification of skin tumors [1], since one of us (BZ) was intimately involved in writing that statement.

Many Names

What can we learn from all the synonyms, or are they just a literary exercise from history? The most

common synonym in Europe is *histiocytoma*, and it is the least helpful. The concept of histiocytes (from Greek "to histion" for "tissue") is flawed. What could be less specific than a "tissue cell?" [2]. Most modern classifications today identify 2 types of bone-marrow-derived cells capable of antigen presentation and phagocytosis [3]. The dendritic cells, including the Langerhans cells of the skin, are professional antigen-presenting cells, while the macrophages are primarily phagocytic cells. Early lesions of DF [4] may be rich in macrophages; these cellular variants are what has been called histiocytoma; later as both cellular and fibrous elements are seen, the term *fibrous histiocytoma* may be used [5].

Many other cells may be present, including neutrophils, lymphocytes, and occasionally eosinophils and mast cells. Variable presence of these inflammatory cells and trauma lead to *pseudolymphomatous dermatofibroma* [6], *dermatofibroma with diffuse eosinophilic infiltrate* [7] and *lichenoid, erosive,* and *ulcerated variants* [8].

Later lesions of DFs have few cells and consist mostly of fibrocytes and collagen; in addition, endothelial cells, nerves, and smooth muscle fibers may be involved. Such lesions have been termed *fibroma durum, subepidermal nodular fibrosis or sclerosis* [9], and even *sclerotic* or *sclerosing fibroma* (synonym: storiform collagenoma) [10] or *keloidal dermatofibroma* [11]. Sometimes the endothelial cells are very prominent; this may explain the now extinct name of *sclerosing hemangioma* [12]. In our opinion, *dermatofibroma* is the most appropriate term, both clinically as well as pathologically.

Etiology

Our concept is that DFs are a local response to some type of inflammation or trauma—be it an arthropod bite reaction, a ruptured hair follicle (these are the 2 most common), a ruptured follicular cyst, a viral wart, or foreign bodies such as a wood splinter or suture material. Initially, there is an inflammatory response with granulation tissue, neutrophils, macrophages, lymphocytes, and fibroblasts, whereas later the reparative fibrous response dominates. Fibroblasts are activated fibrocytes that present as epithelioid cells with round to oval, hypochromatic nuclei and ill-defined cytoplasm in a loose stroma of mucin, but no or only minor amounts of thin collagen bundles. On H&E such cells are frequently difficult or impossible to differentiate from macrophages, Langerhans cells, activated endothelial cells, or other epithelioid cells. Immunohistochemically, they are positive for vimentin, while markers for other lines of differentiation are negative. The only exception are myofibroblasts which immunohistochemically are positive for smooth muscle specific actin; histologically, they are somehow halfway in between fibroblasts and fibrocytes, i.e., spindly cells with long cytoplasmic extensions and slender elongated nuclei. In contrast to fibrocytes their cytoplasm is more prominent and brightly eosinophilic, which is due to the presence of the contractile components. On the other hand fibrocytes are slender spindly to wavy cells with hyperchromatic nuclei, moderate amounts of cytoplasm, and embedded into a stroma with more or less prominent/thick collagen bundles, which may become wiry, storiform and/or sclerotic [13].

A single process, a fibrosing dermatitis [5], is seen and described at different moments of its life history. More than a quarter-century ago, one of us (WB) [14] was convinced he had identified 4 patterns in DF: cellular, fibrous, mixed, and lacy vascular. After selecting 200 DF, we sectioned through the blocks, preparatory to doing the first immunoperoxidase studies on so-called fibrohistiocytic lesions. To our chagrin, we saw that the patterns were not even consistent within a given lesion but varied as one cut through the block. The lacy vascular pattern was simply the periphery of the lesion. We suspect many other patterns are also focal or represent just 1 stage in the life of a DF. The attentive reader will find this motif continuously throughout this paper.

Stereotypical Clinical Features

What is the clinical relevance of a DF? It is clearly the most common fibrocytic lesion, except for scars [13]. It may develop at any age; nearly every adult has at least 1. There is a wide variety of clinicopathologic variants (Table 1), which in a minor proportion of cases (2–3%) may cause difficulties in correct interpretation and subsequently lead to clinical mismanagement such as further or even wide excisions, superfluous internal investigations, long-term follow-up, stigmatization of patients with a malignancy, and unnecessary costs [15].

The most characteristic setting is on the shins or calves of young adult females. Usually, a DF is a single, round, oval to targetoid slightly elevated papule (Fig. 1a). Early lesions are red or red-brown; older ones, brown to skin-colored, frequently with a darker peripheral rim. Lesions are moderately well circumscribed and firm. Marked hemorrhage may make the lesions darker producing a *hemosiderrhotic dermatofibroma* [16]. Those that are lipid rich have a

Table 1. Clinicopathologic Characteristics of Dermatofibroma (DF) Variants

DF Type/Variant	Predilection Sex, Age, Site	Clinical Pitfalls	Histopathologic Pitfalls
Variants with prominent architectural (low-power) peculiarities:			
Deep penetrating DF	F, 20-40 upper & lower limbs, trunk	DFSP	DFSP
Plaque-like dermal fibromatosis, dermatomyofibroma	F=M, 10-30, shoulder, proximal extremities	DFSP	Fibromatosis
Atrophic DF	F, 20-40, shoulder	Basal cell carcinoma	
Aneurysmal FH	F, 20-40, lower legs	Hemangioma, melanoma	Kaposi sarcoma
Haemangiopericytoma-like FH	F, 20-40, lower legs	Hemangioma, melanoma	Infantile myofibroma(tosis)
Palisading cutaneous FH	F, 20-40, hands & feet		Schwannoma
Lichenoid, erosive, & ulcerated DF	F, 20-40, lower legs		
Variants with prominent cytologic or stromal (high-power) peculiarities:			
Clear cell DF	F, 20-40, lower legs		Renal cell carcinoma metastasis
Granular cell DF	M, 20-40, shoulder		Granular cell tumor
Myofibroblastic DF	F, 20-40, lower legs		Myofibroblastoma
Sclerotic DF	F, 20-40, acral	Indicator of Cowden syndrome	
Keloidal DF	F, 20-40, upper & lower extremities		Keloid
Atypical/pseudosarcomatous FH, DF with monster cells	F, 20-40, lower legs		Atypical fibroxanthoma
Hemosiderrhotic DF	F, 20-40, lower legs	Melanoma	Melanoma
Cholesterotic/lipidized DF	F, 20-40, ankle		Gout
Myxoid DF	F, 20-40, hands & feet		Myxoma, mucous cyst
Ossifying DF	F, 20-40, lower legs		Extraskeletal osteosarcoma
Pseudolymphomatous DF	F, 20-40, lower legs		Pseudolymphoma
DF with diffuse eosinophilic infiltrate	F, 20-40, lower legs		Langerhans cell disease
Variants with architectural (low) and cytological or stromal (high-power) peculiarities:			
Epithelioid cell histiocytoma	M, 10-30, upper limbs	Spitz nevus	Spitz nevus
Cellular benign FH	M, 10-30, limbs, head, neck		Dermal leiomyosarcoma
Smooth muscle proliferation in DF	F, 20-40, ankle		Infantile myofibromatosis
Multinucleate cell angiohistiocytoma	F, 40-70, face, acral sites	Sarcoidosis, Kaposi sarcoma, tufted angioma	Kaposi sarcoma
Cellular neurothekeoma	F=M, 10-30, upper limbs and trunk, face		Myxoid neurothekeoma/nerve sheath myxoma
Combined DF	F=M, 40-60, lower extremities, face, trunk		Miscellaneous entities

Dermatofibrosarcoma protuberans (DFSP), fibrous histiocytoma (FH).

yellow hue and are more common about the ankle; they have been called *ankle-type dermatofibroma*. Cystic lesions may be soft. Trauma may produce eroded or crusted nodules or tumors.

The "dimpling" or Fitzpatrick sign, when lesions are squeezed between the thumb and index finger, is characteristic. Thereby smooth pressure forces the DF down into the subcutis; this phenomenon is caused by the altered arrangement of collagen in the reticular dermis.

Clinical Variants

There are many clinical variants of DF, which may cause differential diagnostic problems, as shown in Table 1, which also includes some of the unusual microscopic features considered below. Some DFs are quite exophytic as in *epithelioid cell histiocytoma* (Fig. 1b), which is usually a red-brown dome-shaped papule mistaken clinically and even histologically for a Spitz nevus [17].

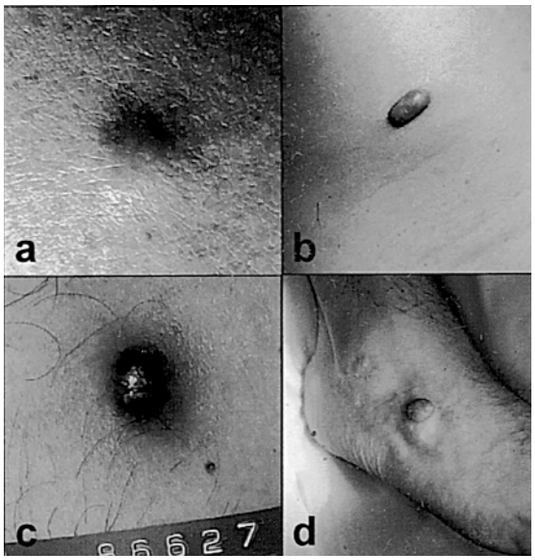

Fig. 1. a. Ill-defined, slightly brown papule of dermatofibroma. **b.** Exophytic papule of epithelioid cell histiocytoma. **c.** Bluish-black nodule of aneurysmal fibrous histiocytoma. **d.** Exoendophytic tumor of a deep penetrating dermatofibroma.

Atrophic dermatofibroma [18] also has a distinctive clinical presentation. Most commonly adult women present with skin-colored plaques on the trunk, in particular the shoulder girdle, clinically interpreted as a basal cell carcinoma. Histology reveals a characteristic DF where shrinkage of fibroplasia has flattened the lesion, which becomes substantially thinner than the surrounding dermis. Similar lesions can sometimes be observed on the shins or calves.

A solitary *sclerotic DF* [10] is never identified clinically. On the other hand, patients with Cowden syndrome have multiple often acral sclerotic DFs, which are never identified as DF, but instead described as "acral papules" or something equally vague. These lesions most likely represent regressing or fibrotic human papillomavirus (HPV) infections, as patients with Cowden syndrome have other warty lesions, such as trichilemmomas [19].

DFs usually are long-standing lesions that cause no complaints, except *aneurysmal fibrous histiocytoma* [20,21] (Fig. 1c). The latter may rapidly enlarge because of spontaneous or traumatic hemorrhage into a previously asymptomatic lesion and frequently is painful. Such lesions can clinically sometimes be misinterpreted as angiomas or melanomas. Histologically, a nodule of spindle cells with hemorrhage can mimic nodular Kaposi disease, or, when lesions get older and show siderophages, misinterpreted as melanophages, sometimes even melanoma. Immunohistochemistry is helpful as both vascular markers such as CD31 and CD34 and all melanocytic markers are negative.

Angiomatoid fibrous histiocytoma is a confusing synonym that should not be used for this DF variant. The term should be restricted for a lesion that previously was known as *angiomatoid malignant fibrous histiocytoma* [22]. Akin to aneurysmal fibrous histiocytoma, this lesion shows prominent hemorrhage but nests to sheets of epithelioid cells with some moderate atypia characteristically positive for desmin and S100 protein. Most of these lesions occur in children, may recur, and even extremely rarely metastasize. In the last WHO classification on soft tissue and bone tumors [23] these were downgraded from the high to the intermediate group of fibrohistiocytic lesions.

Still other DFs are larger, forming nodules or plaques. Large flat plaques up to more than 20 cm in diameter [24], which may also show satellite papules, and deep penetrating dermatofibromas (Fig. 1d) [25,26] may both be confused with dermatofibrosarcoma protuberans. Such lesions have been grouped together as giant DFs [27]. Histology usually shows stereotypical features of DF, in case of deep penetrating DF with superficial involvement of subcutaneous fat septae more than lobules.

Occasionally, there may be a few, up to several dozen, sometimes grouped ("agminated") papules [5]. Multiple widespread DFs are regarded as a marker of immune suppression; they have been observed most often in black females with systemic lupus erythematosus but are also seen in patients with HIV/AIDS, other autoimmune diseases (Sjögren syndrome, pemphigus vulgaris, myasthenia gravis, and ulcerative colitis), and in those with iatrogenic immunosuppression such as transplant recipients.

Macroscopy

DF may have a distinct appearance when sectioned before histologic preparation. The cut surface of the firm papules often has a distinctive yellow color, which may show areas of hemorrhage and lipidization. Prominent lipophages are seen in *fibrous xanthomas* [5]; xanthomatized macrophages are due to lipids from lipid membranes of extravasated erythrocytes or from involvement of the subcutaneous fat. This is particularly prominent in *cholesterotic* [28] or *lipidized* [29] *fibrous histiocytoma*, which, owing to its special, trauma-favoring location, is also known as ankle-type DF.

Stereotypical Histology

DFs show a dense infiltrate of fibrocytes and/or macrophages in the reticular dermis, and, sometimes, the upper part of the subcutis. Early lesions are rich in macrophages, some of which may be siderophages, and/or lipophages, others multinucleate, e.g., Touton or foreign body giant cells. At times foam cells may be prominent in deeper areas adjacent to subcutaneous fat. Late lesions (Fig. 2) show prominent fibrocytes and coarse bundles of collagen in a haphazard fashion, frequently arranged in short fascicles that interweave ("storiform"), sometimes with a sclerotic center. Lesions are ill defined owing to splaying of both fibrocytes and macrophages between thickened collagen bundles at the periphery of the lesion (often called "entrapment of collagen"). Epidermal, melanocytic, and folliculosebaceous hyperplasia is characteristically found above the lesions, while rarely smooth muscle or neural proliferation is observed [30]. The epidermal hyperplasia is most common and can be so prominent that buds of hair follicles mimic superficial basal cell carcinoma [31]. It may be minimal or absent in late or deep-seated lesions. Lymphocytes are often spread throughout the lesion with frequent prominence at the periphery but may be lacking in later stages.

Histologic Variants

A wide variety of histologic variants of DFs has been proposed [32]. Apart from unusual architecture, as alluded to under clinical variants (Figs. 3, 4), DFs may present with stromal and cellular peculiarities. Antler- to staghorn-like vascular ectasia in a lesion with dense cellularity has been described as *hemangiopericytoma-like fibrous histiocytoma* [33]. In other instances lamellar and storiform fibrosis surrounded by palisades of fibrocytes mimics schwannoma. This has been described as *palisading dermatofibroma* of the hands and feet, where such lesions are most frequently encountered [34]. Similarly, *myxoid dermatofibromas* [35,36] (Fig. 5) are most commonly seen on the hands and feet, in particular on the fingers and toes. Such lesions reveal the typical silhouette of a DF, yet the collagen bundles are less thick and storiform, but separated by vast amounts of mucin. There may be some relation to mucous cyst of the finger, which may be another trigger of a DF-like response.

Rare cases of *ossifying dermatofibroma* reveal bone formation with osteoclast-like giant cells [37]. In our experience subungual osteochondroma (syn-

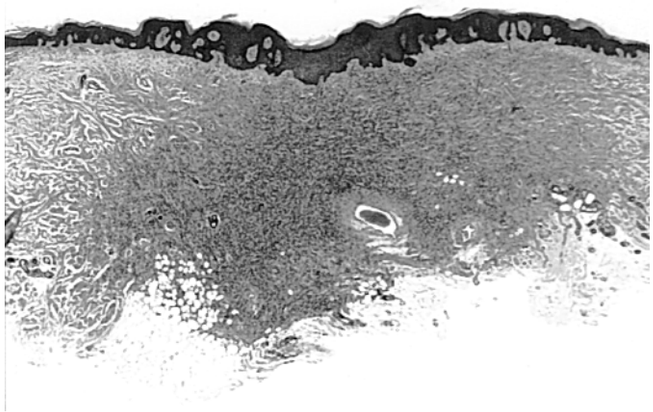

Fig. 2. Characteristic silhouette of dermatofibroma.

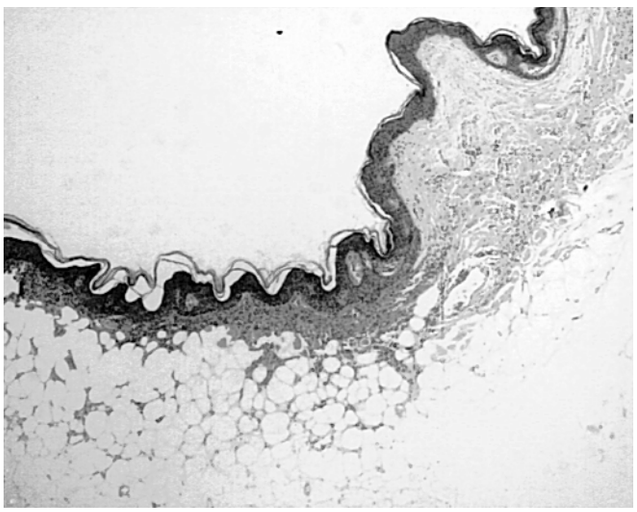

Fig. 3. Dermal atrophy in atrophic dermatofibroma.

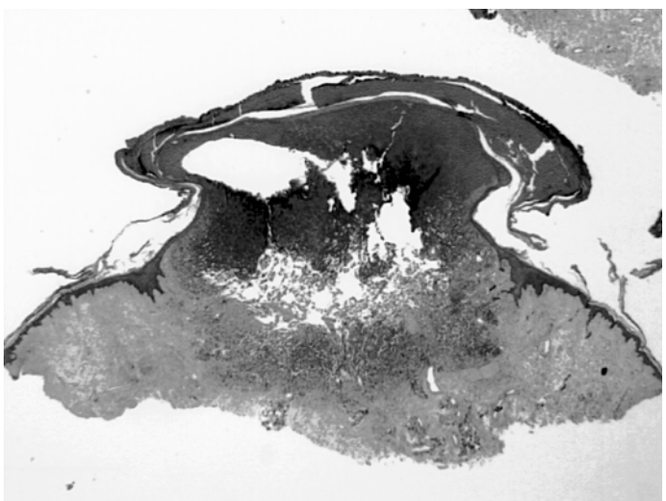

Fig. 4. Hemorrhage and pseudovascular clefts in aneurysmal fibrous histiocytoma.

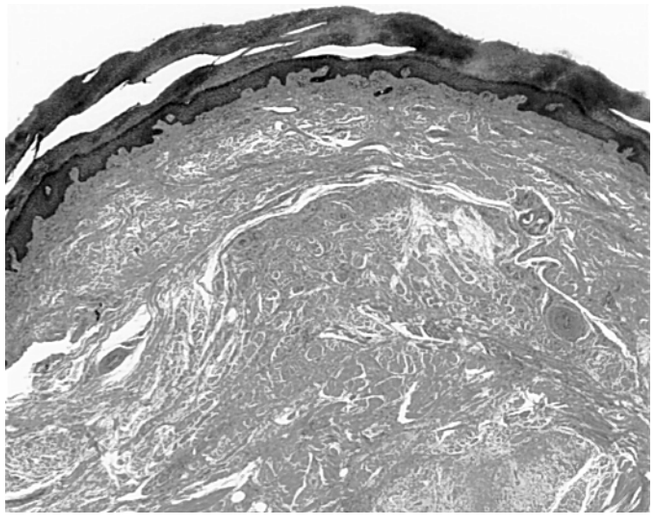

Fig. 5. Prominent mucin in myxoid dermatofibroma.

onyms: subungual exostosis and fibro-osseous pseudotumor of the digit) [13] overlaps with or is intimately connected with subungual or acral counterparts of dermatofibroma. Peripheral ossifying fibroma in the oral cavity is a DF-like lesion that invariably contains bone. The special anatomy with bone and cartilage close to the skin or mucosa and the susceptibility to trauma are responsible for the involvement of these components in otherwise typical fibrosing inflammation.

The various types of superficial fibromatoses [13] such as palmar Dupuytren contracture, plantar Lederhose disease, or penile Peyronie contracture all share features with DF. They can be interpreted as late-stage variants of such a fibrosing process complicated by the sequelae of shrinkage. In contrast, in the subcutis or deeper tissues the more loose tissue conditions give rise to other presentations: "connective tissue culture"-like appearance in nodular fasciitis; or with epithelioid, sometimes giant cells with homogenous cytoplasm ("ganglion"-like cells) in proliferative fasciitis; or with analogous features in deep muscle tissue as proliferative, sometimes ossifying myositis [13].

Unusual cytologic features of DFs include *epithelioid cell histiocytoma* [17,38] with scalloped eosinophilic cells, which may mimic Spitz or other types of nevi, yet never express melanocytic markers such as S100 protein, HMB45, or Melan A (A103). It has been suggested [17] that the location in the papillary dermis with a moderate amount of loose collagen fibers allows cells more easily to develop epithelioid features than in the reticular dermis where the much more restricted tissue constrictions favor a spindle-cell appearance. Alternatively, the age of a lesion may play a role, so that early phases show epithelioid fibroblasts, whereas in later stages spindle cells are seen.

While most of these lesions are confined to the papillary dermis with a prominent collarette of epidermis and adnexal epithelium lateral to the exophytic papule, some lesions can extend deeply into the reticular dermis and even subcutis, either diffusely or with fascicles or nests. In our experience such deep penetrating epithelioid cell histiocytomas (Fig. 6) are part of the spectrum known in the literature as *cellular* or *atypical benign fibrous histiocytoma*

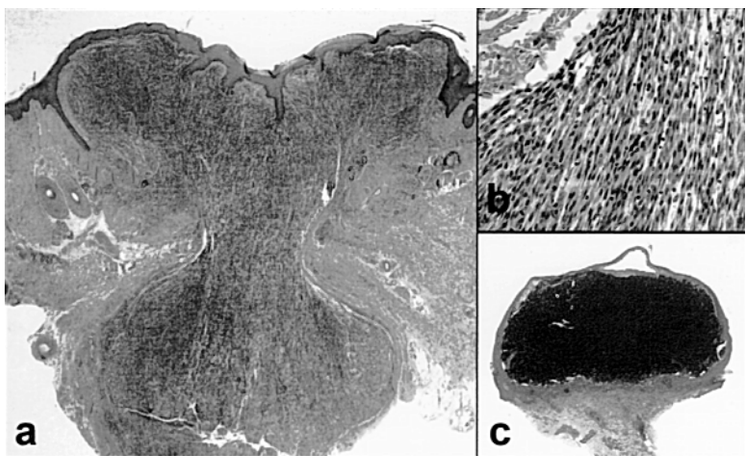

Fig. 6. a. Cellular benign fibrous histiocytoma. **b.** With deep penetrating fascicles of dense cellularity and numerous mitoses ("combined dermatofibroma"). **c.** Reactivity for factor XIIIa in epithelioid cell histiocytoma.

[39], most commonly located on the trunk, back, and upper arm, and frequently misinterpreted as fibro-, leiomyo- or even angiosarcomas, the latter in particular when additional hemorrhage is prominent.

In *clear cell dermatofibroma* [40,41] (Fig. 7), epithelioid fibrocytes show an ill-defined, empty cytoplasm interspersed by thickened collagen bundles. Together with epidermal and melanocytic hyperplasia and some moderate lymphocytic response, this gives the vague silhouette of a DF. Because of prominent vascularization, such lesions are frequently thought to represent metastases from renal cell carcinoma. They are negative for keratin markers. Some clear cell DFs focally show a PAS-positive granular cytoplasm akin to that of *granular cell dermatofibromas* [42]. The latter occur predominantly on the shoulder girdle and are indistinguishable from "ordinary" granular cell tumors except that they stain negative for S100 protein. Fibrocytes are epithelioid and show a prominently granular eosinophilic cytoplasm with considerable variation in the size of granules, some of which measure nearly half the size of erythrocytes. Again architectural criteria of collagen entrapment, epidermal and melanocytic hyperplasia, and a moderate infiltrate of demarcating and intermingled lymphocytes, as well as the S100 protein negativity, are helpful for diagnosis.

Apart from all these individual variations, some lesions may show a combination of several unusual clinical and histopathologic features, e.g., deep penetration and epithelioid cells (Fig. 6); recognition of such *combined dermatofibromas* [15] allows the histopathologist to apply a confident benign label to unusual lesions.

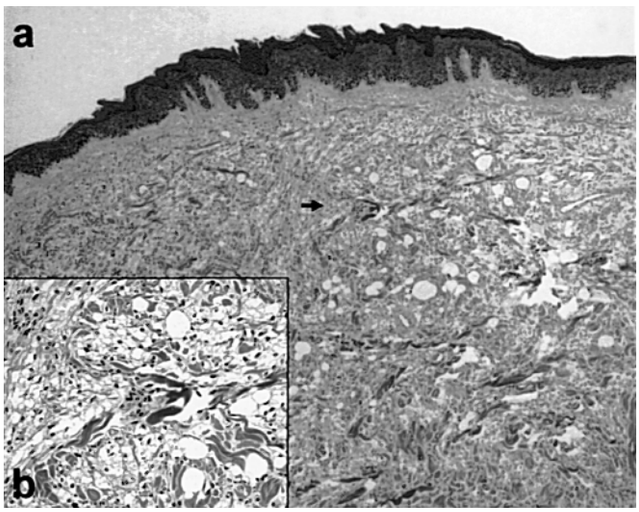

Fig. 7. a. Clear cell dermatofibroma with epidermal hyperplasia. **b.** Typical cytology beside prominent collagen bundles.

Differential Diagnoses

The most important histologic differential diagnoses are dermatofibrosarcoma protuberans and Kaposi sarcoma. *Dermatofibrosarcoma protuberans* is poorly circumscribed, usually much broader and deeper with irregular dissection of subcutis, and shows cells with wavy nuclei in association with delicate fibrillary bundles of collagen frequently arranged in a storiform pattern. In contrast to DF it is regularly positive for CD34. *Kaposi sarcoma* in nodular and tumor stage is characterized by erythrocytes extravasated into slits between interweaving fascicles of spindle-shaped cells; often, tiny pink hyaline globules that represent degenerated erythrocytes are found in these spindle-shaped endothelial cells. Lesions are positive for CD34 and vascular markers such as CD31. In times before immunohistochemistry and modern techniques such as polymerase chain reaction (PCR) which can detect human herpesvirus 8 (HHV8) in Kaposi lesions, differentiation of nodular Kaposi sarcoma from aneurysmal fibrous histiocytoma was sometimes a difficult task.

Immunohistochemistry

Immunohistochemistry has failed to produce a simple reproducible profile to allow the unequivocal diagnosis of DF. Instead DF reveals a variable immunohistochemical profile that reflects the stage of the inflammatory response [24]. Early lesions are rich in reactivity for macrophage markers such as KiM1p, PGM1, or KP1 (CD68). Variable reactivity is seen for lysozyme, trypsin, and chymotrypsin. Macrophages are important to remove foreign body material including sebum, hair, and the various commensals housing in the folliculosebaceous units as well as tissue necroses, in particular when abundant erythrocyte extravasates are present or subcutaneous tissue is involved.

Xanthogranulomas are inflammatory lesions dominated by macrophages [43], which sometimes are difficult to differentiate from DF or one of its variants, e.g., epithelioid cell histiocytoma from scalloped cell xanthogranuloma; "ordinary" DF from spindle cell xanthogranuloma; or fibrous xanthoma from papular xanthoma, another variant of xanthogranulomas dominated by xanthomatized macrophages. Both entities, dermatofibromas and xanthogranulomas, also share frequent labeling for

factor XIIIa in early phases (Fig. 6c). Labeling for factor XIIIa indicates activity of a protease involved in tissue linkage mechanisms, e.g., covalently connecting the numerous monomer structures of fibrin and collagen [44]. This reactivity is mostly seen at the periphery and continuously diminishes with the aging of the lesion to be completely absent in atrophic variants.

Predominance of factor XIIIa-positive dendritic cells has given raise to the concept of *dermal dendrocytomas* [45,46]. In our experience dermal dendrocytomas are just another variation on the theme of an early fibrosing dermatitis, which consists of a variably mixed population of fibrocytes and dendritic macrophages positive for factor XIIIa. Langerhans cells are not a predominant cell type of these lesions, but frequently may be scattered through the lesion, as shown by cells positive for CD1a dispersed in a starry sky pattern.

A time cycle in the profile of an immunohistochemical marker is also observed with proliferation markers such as proliferating cell nuclear antigen, Ki-67 (Mib1), and labeling for antimetallothionein [24]. Rapidly evolving lesions such as early DFs show prominent mitoses, while sclerotic variants have none. Antimetallothionein labeling of early lesions may best be explained by metabolically active tissue reactions that need many enzymes (e.g., DNA-polymerase) dependent on trace elements such as copper or zinc delivered by the apoprotein family of metallothioneins [47].

Other variably expressed markers include smooth muscle-specific actin, NKIC3 (CD56), and NSE. Labeling for smooth muscle-specific actin is most prominently seen in *myofibroblastic dermatofibroma* [48], which shows slim, spindle-shaped nuclei with slender cytoplasmic cell extensions. NKIC3 or 123C3 (CD56) is encountered in 10% to 20% of all DFs, at least focally, and in particular and frequently very prominent, in those with myofibroblastic, granular, and clear cell differentiation. Our experience is similar with neuron-specific enolase (NSE) [48]. Variable reactivity is seen with vascular markers such as factor VIII or CD31. Exceptional cases with characteristic histologic features of DF show diffuse reactivity for CD34 [49,50]; other rare cases express S100 protein.

Ultrastructure

Ultrastructural findings correlate with the histologic and immunophenotypic findings. Thus, macrophages are characterized by large euchromatic to hypochromatic nuclei with prominent nucleoli, prominent endoplasmic reticulum, and numerous phagolysosomes. Phagosomes and phagolysosomes may reveal hemosiderin or cholesterol clefts. Fibrocytic lesions contain slender, hyperchromatic nuclei, endoplasmic reticulum, and prominent collagen around the slender cells. The latter cells may show focal or more prominent basal lamina formation as well as fibrillary structures, focally condensed to attachment plaques of myofibroblasts [48].

Prognosis

We view DF as an entirely benign reactive process [51], which when incompletely excised may persist. Yet, there are claims that DFs are a neoplasia [52], which may even metastasize (*"metastasizing dermatofibroma"*) and potentially kill the patient [53–55]. This interpretation is supposed to be substantiated by recent cytogenetic FISH and reverse transcriptase PCR (RT-PCR) [56] and molecular studies by HUMARA technique [57], which have documented clonality in a minority of lesions [58]. Clonality alone is by no means proof of a neoplastic disease as it is for example seen in a variety of inflammatory disorders including atopic dermatitis, lichen sclerosus atrophicans, or psoriasis [51].

Both recurrences and rare metastases have been described in *"atypical benign fibrous histiocytomas"* [39] and some forms of *"facial dermatofibromas"* [59]. None of the publications that we are aware of unequivocally document the "progression" of a DF into a malignant process. Authors may show medium- or high-power views with bland features and say that these lesions were clonal, recurred, or even metastasized; or they show atypical areas with high cellularity, atypia, mitoses, and even necroses taken from lesions that behaved in a benign fashion. Consistently missing is a scanning magnification, which would permit use of architectural criteria for differentiation of a benign fibrosing dermatitis from a malignant neoplasia.

Rarely one may encounter long-standing, huge (up to 25–30 cm), ill-defined lesions, which may be multinodular, protuberant, or eroded. Multiple sections show features of dermatofibroma. Even immunohistochemistry for CD34 is negative. We have struggled with such lesions, have seen similar cases presented, but are unaware of any published reports. In our interpretation this is a form of fibrosarcoma that closely mimics dermatofibroma. One must combine the clinical picture and the macroscopic presentation and perform extensive sampling. Such lesions frequently are acral, some-

times also facial, and may show nail and bone destruction on x-ray film. Histology reveals ill-defined, irregular nodules to tumors with high cellularity; single and mass necroses; destruction of preexisting structures such as epidermis, adnexa, nail, or bone; variable atypia; and atypical mitoses. Clinically, they grow slowly, but insidiously, frequently recur, and, when not adequately excised with margins of 2 to 3 cm, may develop metastases to lymph nodes, lungs, and other internal organs.

These features must not be confused with *dermatofibromas with monster cells* [60] or *atypical /pseudosarcomatous fibrous histiocytomas* [61] (Fig. 8). In our experience these are ancient/degenerative features in long-standing lesions; they always behave in a benign fashion, and do not histologically show high cellularity, necroses, and atypical mitoses. These lesions must also be differentiated from *atypical fibroxanthomas*, but here growth pattern, cytologic atypia, numerous mitoses, and greater prominence of xanthomatized macrophages allow easier separation.

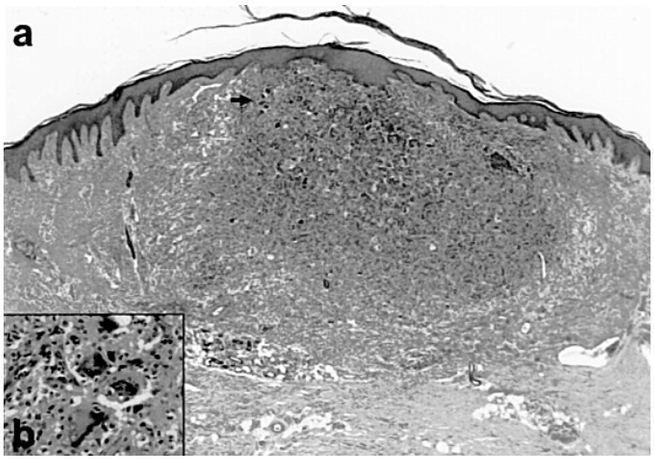

Fig. 8. a. Atypical/pseudosarcomatous fibrous histiocytoma with typical silhouette of dermatofibroma. **b.** Prominent atypia including monster cells.

Special Variants

Three lesions are not generally accepted as DFs, but we feel show many features. We recognize that others disagree with this assessment. Nonetheless, by considering the possible relationship of these 3 lesions to DF, we may learn a bit more about all these lesions.

Multinucleate cell angiohistiocytoma [62] is a characteristic clinicopathologic entity that occurs on the trunk or proximal extremities of young adults with clusters of bluish-brown papules. Clinically, sarcoidosis or Kaposi sarcoma are most frequently suspected. Histology of every single papule reveals a silhouette with features of an unusual dermatofibroma: epidermal and melanocytic hyperplasia, increase of spindle cells in a fibrosclerotic stroma, variable lymphocytes, and, most characteristic, ectatic vessels and multinucleate giant cells. One could view these lesions as combined dermatofibromas consisting of grouped papules with features of sclerosing hemangioma and bizarre giant cells of dermatofibroma with monster cells. Similar papules are sometimes seen close to plaque-like variants of dermatofibroma [24].

Plaque-like dermal fibromatosis [63] or *dermatomyofibroma* [64] is a clinicopathological entity characterized by papules to sometimes large plaques (up to 10 cm in diameter) with horizontal arrangement of fibrocytes, sparing of adnexal structures, and prominent smooth muscle actin reactivity indicating myofibroblastic differentiation. Again, in our experience, all these features can occur in DF—plaques are characteristic of plaque-like dermatofibroma on the trunk and proximal extremities; horizontal arrangement of fibrocytes and sparing of adnexal structures are also seen in atrophic dermatofibromas, which show predilection for the shoulder girdle; and reactivity for smooth muscle-specific actin is most prominent in rare myofibroblastic dermatofibroma, which also tends to involve the upper trunk. Presumably, this indicates another variation of combined dermatofibroma.

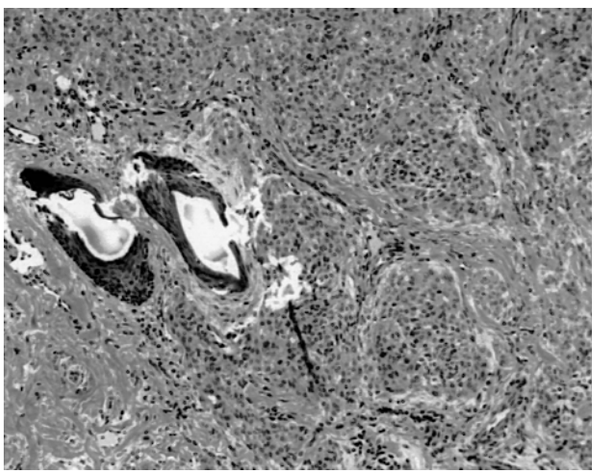

Fig. 9. Cellular benign fibrous histiocytoma with areas imitating cellular neurothekeoma.

Cellular neurothekeomas [65] are dermal lesions that reveal a plexiform architecture with whorled nests of epithelioid cells interspersed and sur-

rounded by thickened bundles of collagen. These cells are similar to epithelioid cells of epithelioid cell histiocytoma [66] and also may show reactivity with NKIC3 (CD56) and for factor XIIIa; in addition smooth muscle-specific actin is seen in roughly one third of lesions. Variable epidermal and melanocytic hyperplasia, as well as lymphocytes demarcating and infiltrating the lesions, are present. Remarkably, cellular neurothekeoma has never been observed outside the dermis. Most instructively, cellular neurothekeomas occasionally show transition to areas with features more commonly associated with DFs (Fig. 9). Thus, in our experience, cellular neurothekeoma could be a variant of dermatofibroma or, maybe better, of epithelioid cell histiocytoma [67]. Cellular neurothekeoma stereotypically affects children and young adults on the proximal extremities or in the face; probably, the more loose texture of the reticular dermis in these areas is in favor of a plexiform growth along preexisting vascular structures. Yet, interpretation as a fibrocytic lesion or even a dermatofibroma is highly controversial [68–73]. Others have favored nerve sheath and smooth muscle differentiation [69], and the new WHO classification on soft tissue and bone tumors [23] lists cellular neurothekeoma as an entity of uncertain histogenesis. Cellular neurothekeoma must be differentiated from myxoid neurothekeoma or nerve sheath myxoma [74], which has been shown to be a myxoid variant of schwannoma [75].

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