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REVIEW

Cutaneous fibrohistiocytic tumours – an update

Boštjan Luzar & Eduardo Calonje[1]
Medical Faculty, Institute of Pathology, University of Ljubljana, Ljubljana, Slovenia, and [1]Department of Dermatopathology, St John's Institute of Dermatology, St Thomas's Hospital, London, UK

Luzar B & Calonje E
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Cutaneous fibrohistiocytic tumours – an update

The term 'fibrohistiocytic' tumour is a descriptive designation without histogenetic connotation for a group of heterogeneous lesions that share morphological features of histiocytes and fibroblasts on light microscopy. However, over the years it has become apparent that many so-called 'fibrohistiocytic' tumours are largely composed of relatively undifferentiated mesenchymal cells, but can also show areas of myofibroblastic differentiation. This review focuses on the clinical and histological features as well as differential diagnosis of so-called fibrohistiocytic tumours. Special emphasis is given to more recently described histological variants of fibrous histiocytoma, e.g. cellular, epithelioid, aneurysmal and atypical fibrous histiocytoma, to angiomatous and plexiform fibrous histiocytoma (plexiform fibrohistiocytic tumour), lesions that are not true variants of fibrous histiocytomas but have erroneously been designated such, and to atypical fibroxanthoma. The literature on metastasizing fibrous histiocytoma is also reviewed.

Keywords: atypical fibroxanthoma, fibrohistiocytic tumours, fibrous histiocytoma – variants, metastasizing fibrous histiocytoma, plexiform fibrohistiocytic tumour, update

Abbreviations: AFH, aneurysmal fibrous histiocytoma; AFX, atypical fibroxanthoma; ANFH, angiomatoid fibrous histiocytoma; AtFH, atypical fibrous histiocytoma; CBFH, cellular benign fibrous histiocytoma; EBFH, epithelioid benign fibrous histiocytoma; EMA, epithelial membrane antigen; HPF, high-power field; MFH, malignant fibrous histiocytoma; PFH, plexiform fibrous histiocytoma; SCC, squamous cell carcinoma; SMA, smooth muscle actin; UV, ultraviolet; WHO, World Health Organization

Common fibrous histiocytoma (dermatofibroma)

CLINICAL FEATURES

Common fibrous histiocytoma (dermatofibroma) generally presents as a slowly growing solitary nodule on the limbs of young to middle-aged adults, especially women.[1,2] The presence of a central dimple on lateral compression has been regarded as a useful sign for its proper clinical recognition.[3] The age distribution is very broad (from 20 to 60 years) and the lesion can develop at almost any location. The overlying skin is often reddish-brown to darkly pigmented and scaly. The size of the lesion is usually <10 mm, but giant dermatofibromas measuring from 35 to 300 mm in diameter have also been reported.[4] The recurrence rate following incomplete excision has been estimated to be <2%.[5]

Address for correspondence: Dr E Calonje, Department of Dermatopathology, St John's Institute of Dermatology, St Thomas's Hospital, Lambeth Palace Road, London SE1 7EH, UK.
e-mail: jaime.calonje@kcl.ac.uk

HISTOLOGICAL FEATURES

The epidermis above the dermal proliferation is usually hyperplastic, accompanied by hyperpigmentation of basal keratinocytes, most commonly over the tips of elongated rete ridges. Proliferation of immature hair follicle-like structures is not infrequent, and can mimic and is often erroneously reported as basal cell

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carcinoma. The papillary dermis is usually, but not always spared, thus forming a so-called grenz-zone or tumour-free zone between the epidermis and the underlying proliferation in the reticular dermis. The defining histological feature of a common fibrous histiocytoma is a proliferation, in varying proportions, of spindle cells forming short intersecting fascicles and histiocyte-like cells, admixed with multinucleated giant cells, inflammatory cells, foam cells and siderophages in the dermis (Figure 1A). A well-formed storiform pattern is usually present only focally. The intervening stroma consists of a proliferation of small capillaries and variable amounts of mature collagen, which may predominate, especially in older lesions. Focal extension into the superficial subcutis is not infrequent. A helpful diagnostic feature found most commonly at the periphery of the lesion is individual collagen bundles surrounded by lesional cells, imparting a somewhat hyalinized appearance to the former (Figure 1B).

Variants of common fibrous histiocytoma

Several other variants of fibrous histiocytoma (dermatofibroma) have been reported and include lipidized (ankle-type),[6] haemosiderotic, keloidal,[7] granular cell,[8] palisading,[9] atrophic,[10,11] clear cell,[12] myxoid,[13] lichenoid,[14] balloon cell,[15] signet-ring cell[16] variants, as well as fibrous histiocytoma with osteoclast-like giant cells,[17] with smooth muscle proliferation,[18] with prominent myofibroblastic proliferation[19] and with intracytoplasmic eosinophilic globules.[20] Although typical histological features of a common fibrous histiocytoma are generally found at least focally (see above), the above-mentioned variants may represent the predominant component of the lesion, making its correct recognition challenging.

Lipidized fibrous histiocytoma usually presents as a solitary exophytic yellow nodule.[5,6] Although initial studies demonstrated a predilection for lower extremities, especially around the ankle (so-called 'ankle-type' fibrous histiocytoma),[5,6] similar site and age distribution as for common fibrous histiocytomas was subsequently demonstrated by Wagamon *et al.*[21] Lipidized fibrous histiocytoma does not appear to be related to hyperlipidaemia.[5,6,21] The lesion is characterized histologically by accumulation of numerous foam cells in the background of hyalinized 'wiry' (Figure 2A), keloid-like and occasionally osteoid-like collagenous bundles. Haemosiderotic fibrous histiocytoma is composed of numerous small vessels, extravasated erythrocytes, and intra- and extracellular haemosiderin deposition due to the haemorrhage (Figure 2B), and probably represents a stage in the development

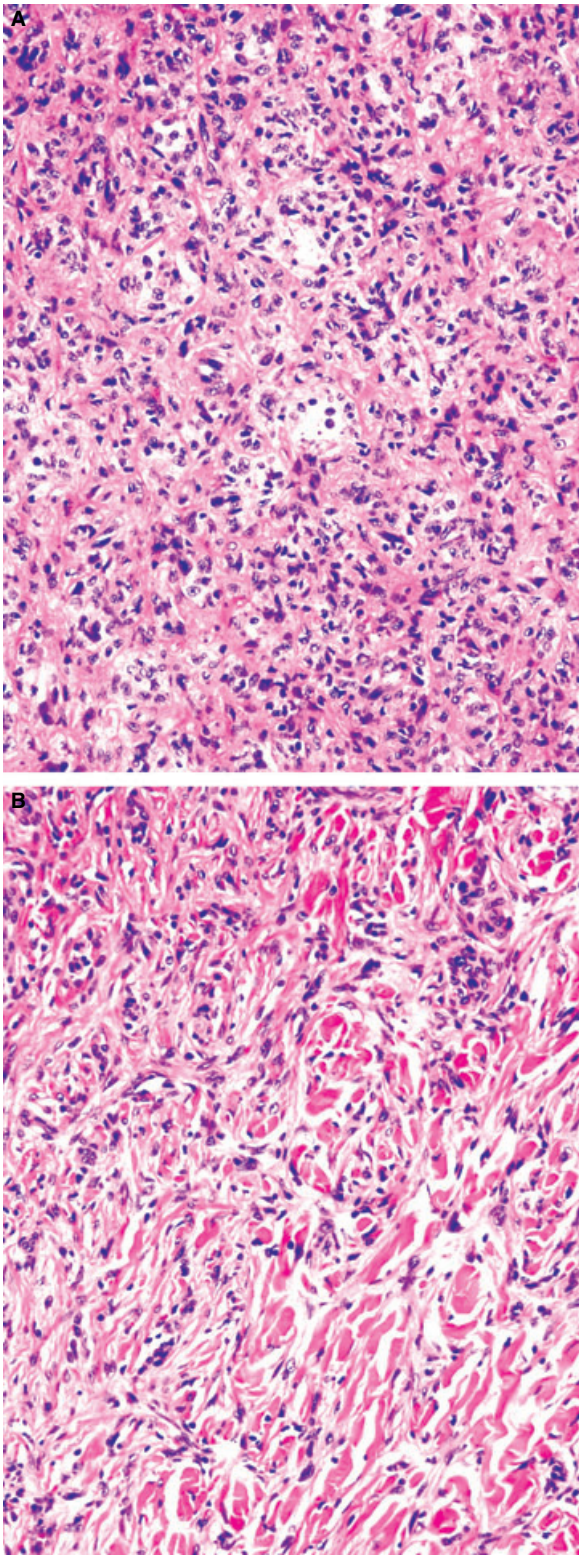

Figure 1. Common fibrous histiocytoma is typically composed of an admixture of histiocyte-like cells (**A**) and spindle cells (**B**). Note globular collagen bundles at the periphery, surrounded by lesional cells, which is a useful diagnostic feature.

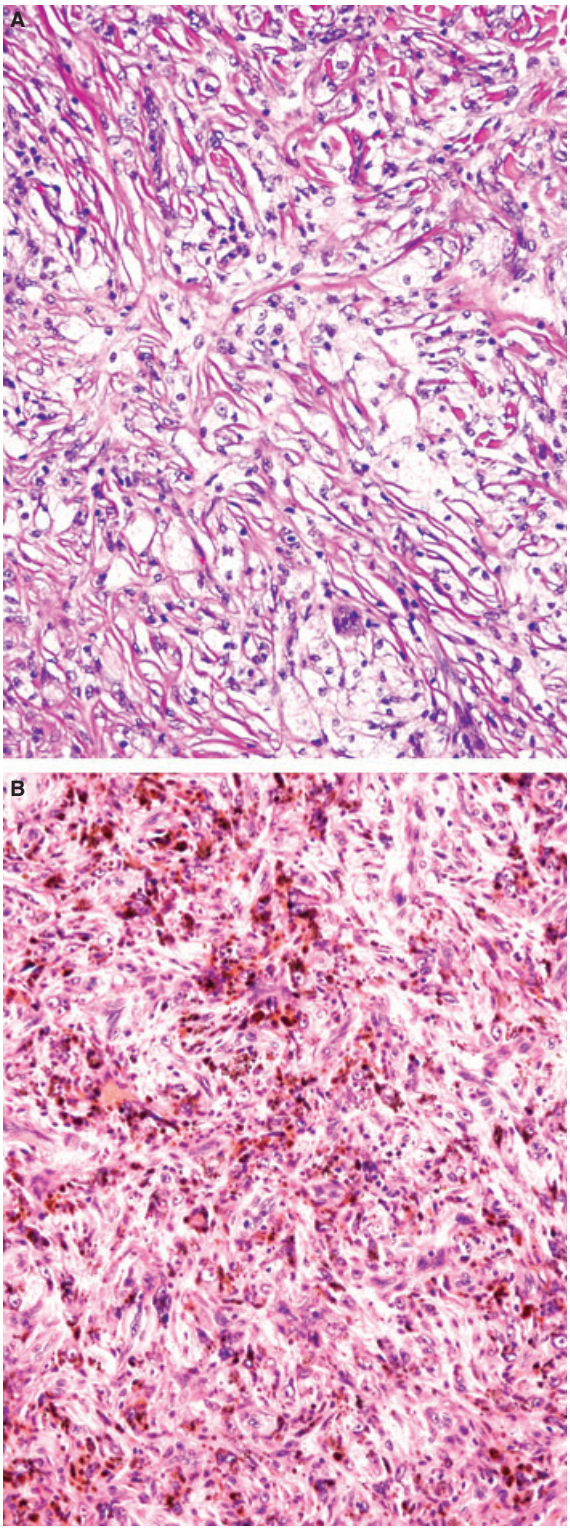

Figure 2. Lipidized fibrous histiocytoma: note foam cells embedded in wiry collagenous stroma (**A**). Haemosiderotic fibrous histiocytoma is characterized by prominent intra- and extracellular haemosiderin deposition, probably representing a stage in the development of aneurysmal fibrous histiocytoma (**B**).

of aneurysmal fibrous histiocytoma (AFH). Keloidal fibrous histiocytoma is composed of irregularly oriented thick collagen fibres mostly in the superficial part of the lesion, surrounded by haemorrhage, haemosiderin and variable numbers of multinucleated giant cells (Figure 3A). Granular cell change is an infrequent phenomenon in fibrous histiocytomas, and is the result of intracellular accumulation of lysosomes (Figure 3B). Palisading fibrous histiocytoma has predilection for the digits, and is delineated histologically by areas of nuclear palisading with formation of Verocay-like bodies.[9] Atrophic fibrous histiocytoma probably represents an end-stage of a common fibrous histiocytoma,[5,11] and can be recognized by varying degrees of dermal atrophy with prominent hyalinized collagen, proliferation of capillaries and low cellularity.[10,22]

Epithelioid benign fibrous histiocytoma

Epithelioid benign fibrous histiocytoma (EBFH) is a distinctive variant of fibrous histiocytoma initially described by Wilson Jones *et al*[23] in 1989 as epithelioid cell histiocytoma. An essentially identical lesion was reported at around the same time as acral histiocytoid haemangioma by Everett and Barr[24], who considered the proliferation to be of vascular origin. The precise histogenesis of the lesion has not yet been elucidated, and an origin from the so-called dermal microvascular unit has been suggested, with differentiation along fibro-histiocytic lineage[25] or myofibroblastic lineage,[26] or both.

CLINICAL FEATURES

EBFH occurs most frequently in the fifth decade of life and shows a slight male predominance (male:female ratio = 1.4:1).[27,28] It generally presents as a solitary, slightly raised or polypoid symmetrical cutaneous papule or nodule of 5–20 mm in diameter. The most frequent site of origin is lower extremity (60%), followed by upper extremity (20%), trunk (10%) and head and neck (<10%).[27–29] A patient with two identical lesions on the nose and arm has recently been reported.[30] Treatment of EBFH consisting of simple conservative complete excision is sufficient. One or even more local non-destructive recurrences have been reported in isolated cases, following incomplete excision.[23,27,28]

HISTOLOGICAL FEATURES

Scanning magnification usually displays architectural features different from those seen in ordinary fibrous

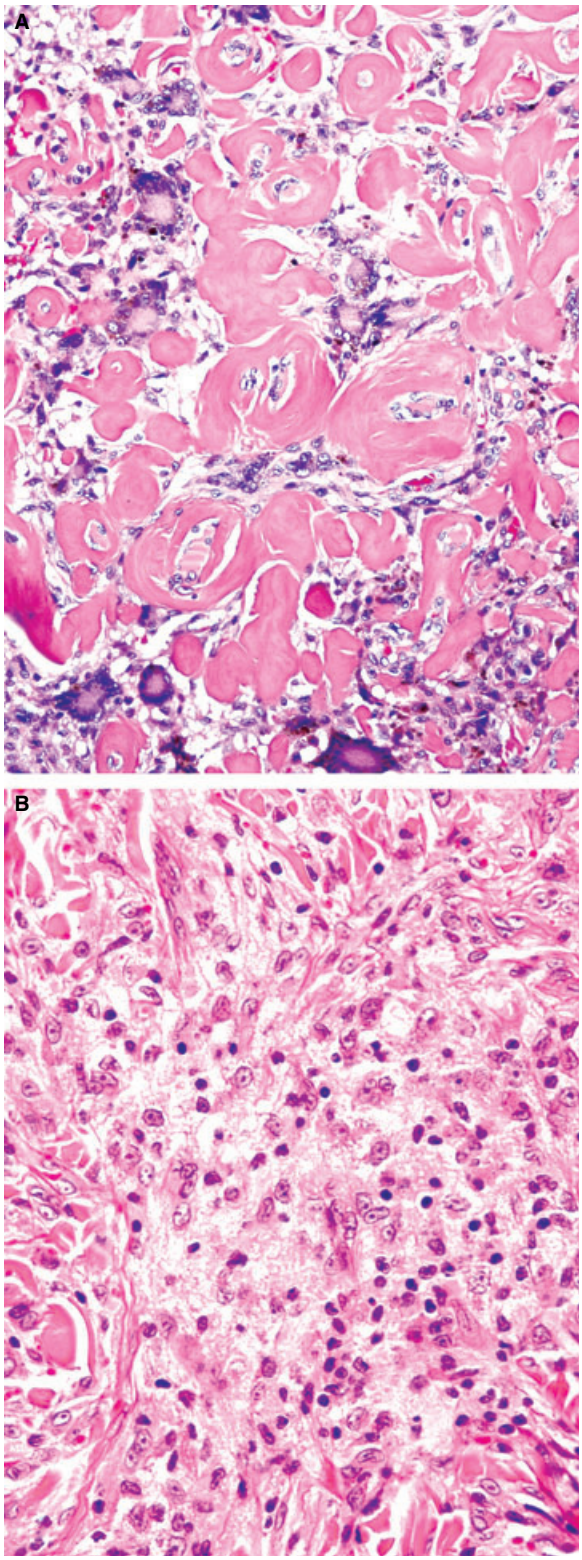

Figure 3. Keloidal fibrous histiocytoma with broad, thick and irregularly oriented collagen bundles, mostly in the superficial parts of the lesion (**A**). Granular fibrous histiocytoma shows prominent granular cytoplasm due to the accumulation of lysosomes (**B**).

histiocytoma. Low-power magnification shows either an exophytic, well-demarcated proliferation located in the papillary and superficial reticular dermis, surrounded by an epidermal collarette (Figure 4A) or, more uncommonly, a slightly less circumscribed and frequently more cellular proliferation extending into the deeper dermis and also into the superficial subcutis. The epidermis above the lesion can be hyperplastic, attenuated, or both. A tumour-free zone between the epidermis and dermis, typical of common fibrous histiocytoma, is generally lacking. By definition, at least 50% of the lesion is composed of rounded or polygonal epithelioid cells with abundant eosinophilic cytoplasm and round to oval nuclei containing small eosinophilic nucleoli (Figure 4B). Mild nuclear pleomorphism is usually present. Occasional regular mitoses can be found, with an average of about one mitosis per 10 high-power fields (HPF) (0.159 mm^2). A variable proportion of binucleate or trinucleate cells is scattered among epithelioid cells, while multinucleated giant cells are usually rare. Lesional cells are separated from each other by delicate collagenous stroma, which, especially in older lesions, may become more hyalinized. Myxoid change may be seen in some tumours and can be prominent and predominate. Adnexal structures are usually not present within the lesion. Numerous small blood vessels dispersed among epithelioid cells are a constant feature, and may on occasion be quite prominent with a haemangiopericytoma-like pattern, essentially mimicking a vascular lesion. In addition to the epithelioid cells, limited amounts of otherwise typical features of a common fibrous histiocytoma can also observed, and include lymphocytes, foamy macrophages and haemosiderin-laden macrophages.

By immunohistochemistry, EBFH contains an admixture of factor XIIIa-positive dendritic histiocytes (so-called dermal dendrocytes) and CD34+ dermal fibroblasts.[25] However, it has been argued that factor XIIIa in EBFH probably delineates reactive cells and not tumour cells.[27] Lesional cells are consistently negative for low- and high-molecular-weight cytokeratins, S100, smooth muscle actin (SMA), desmin, CD31 and epithelial membrane antigen (EMA).[27,28,31] Immunohistochemistry is thus useful in EBFH to exclude its potential histological mimics.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes Spitz naevus, reticulohistiocytoma, juvenile xanthogranuloma and epithelioid perineurioma. In contrast to Spitz naevus, no nesting is present in EBFH, and the cells are consistently negative

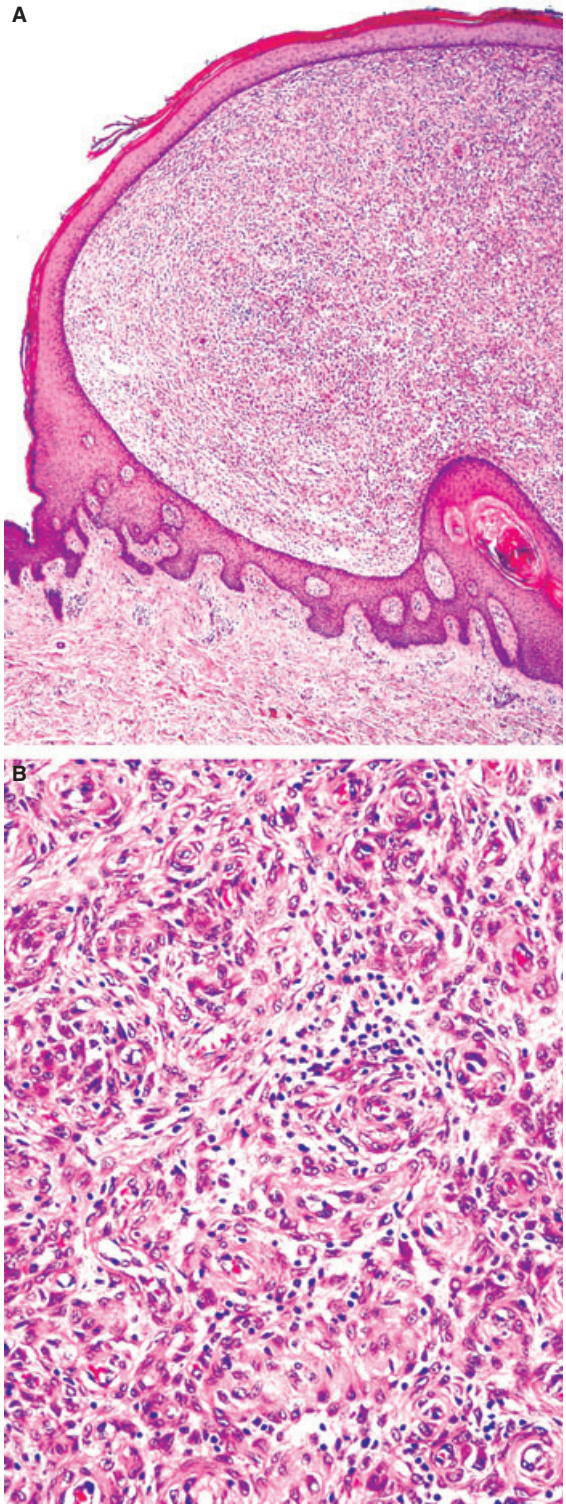

Figure 4. Epithelioid benign fibrous histiocytoma is usually an exophytic polypoid lesion with epidermal collarette extending along the base of the lesion (**A**). Epithelioid benign fibrous histiocytoma is composed of rounded polygonal epithelioid cells with abundant eosinophilic cytoplasm, round to oval nuclei with small eosinophilic nucleoli (**B**). Note proliferation of numerous capillaries.

for melanocytic markers, such as S100, melan A and HMB45. Scattered S100+ reactive dendritic cells are frequently present among lesional epithelioid cells,[27] and should not be misinterpreted as a sign of melanocytic differentiation. Reticulohistiocytoma is characterized by large mono- and multinucleated cells with glassy cytoplasm, admixed with lymphocytes and neutrophils.[26] Juvenile xanthogranuloma typically consists of a proliferation of histiocytes with eosinophilic cytoplasm, admixed with spindle cells, foamy macrophages, multinucleated giant cells, often of the Touton type, as well as inflammatory cells. Although early lesions may lack or contain limited amounts of giant cells, deeper sections frequently highlight the foci of lipidized cells.[28] Epithelioid perineurioma is composed predominantly of cells with round to oval nuclei and abundant amphophilic or eosinophilic cytoplasm, reminiscent of those in EBFH, forming clusters or diffuse sheets.[32] However, consistent EMA and claudin-1 positivity in epithelioid perineurioma and whirling of tumour cells in the latter allow proper recognition of EBFH. It is important to highlight that the amount of EMA protein in perineural cells is often not prominent and positivity in tumour cells may be subtle, consisting of faint immunoreactivity of delicate cytoplasmic processes.

Aneurysmal benign fibrous histiocytoma

Santa Cruz and Kyriakos[33] reported in 1981 a series of 17 cases of a peculiar variant of fibrous histiocytoma that differed in their clinical presentation as well as histological features from common fibrous histiocytoma, and designated the entity an aneurysmal ('angiomatoid') fibrous histiocytoma (AFH). AFH represents <2% of all fibrous histiocytomas.[34] In contrast to common fibrous histiocytomas, which recur exceptionally (in <2%), recurrences following incomplete excision have been reported in up to 19% of AFH.[34] Cytogenetic analysis of a single case of AFH detected translocation t(12;19)(p12;q13) as the sole genetic abnormality.[35]

CLINICAL FEATURES

AFH develops most frequently in the fourth decade of life, with a mean age of about 37 years, and shows female predominance (M:F = 1:1.5).[33,34,36] Although the anatomical distribution is quite broad, AFH shows a predilection for the lower limbs/limb girdle (55%), followed by upper limbs/limb girdle (17%), trunk (12%) and head and neck (4%).[33,34,36] The lesion most commonly presents as a solitary papule of variegated

colour from dark brown to red or blue, ranging in size from 5 to 40 mm.[33,34,36] Multiple lesions in a single patient have also been reported.[37] Rapid recent growth due to haemorrhage in an otherwise longstanding lesion is frequently observed.

HISTOLOGICAL FEATURES

AFH is an ill-defined lesion generally located in the dermis, but may on occasion extend into superficial fatty tissue.[33,34,36] However, extensive infiltration into the subcutis and even into underlying skeletal muscle and the lymph node has been reported.[34] A variable degree of epidermal acanthosis is usually present. A defining histological features of AFH, in addition to features seen in common fibrous histiocytoma, is blood-filled spaces ranging from slit-like to large cavities, reminiscent of cavernous haemangioma.[33] Characteristically, the blood-filled spaces lack an endothelial lining and are thus lined by constituent cells of a common fibrous histiocytoma – histiocytes, siderophages, foam cells, fibroblasts and, occasionally, also giant cells (Figure 5). The blood-filled spaces are usually located within the most cellular areas of the fibrous histiocytoma, which are devoid of collagen and elastic fibres, mostly in the central part of the lesion. However, they may represent the predominant component, making correct recognition of the lesion difficult.[34] Surrounding stroma contains abundant small capillaries with prominent interstitial haemorrhage and haemosiderin deposition. A focal storiform arrangement of fibroblasts and histiocytes, as well as hyalinized bundles of collagen surrounded by lesional cells typical of common fibrous histiocytoma, can be detected, especially at the periphery of the lesion.

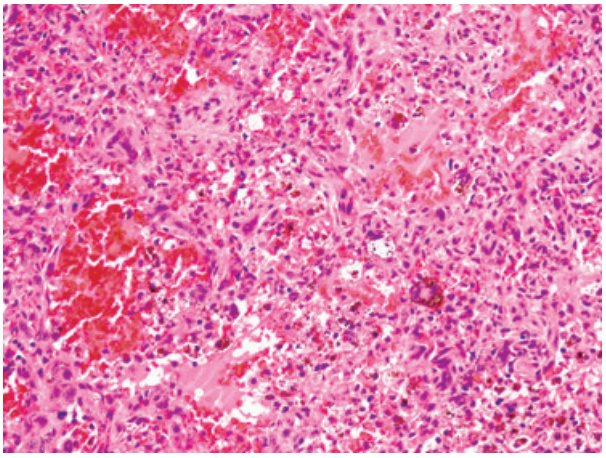

Figure 5. Aneurysmal fibrous histocytoma is characterized by blood-filled spaces reminiscent of cavernous haemangioma that are lined by lesional cells. Note haemosiderin-laden macrophages and multinucleated giant cells.

By immunohistochemistry, focal positivity for SMA may be detected in tumour cells, which are consistently negative for desmin, factor XIIIa, CD34, CD31 and CD68.[34] Factor XIIIa-positive and CD68+ cells in AFH reported in some papers[36,38] may delineate reactive cells within the tumour.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis comprises angiomatoid fibrous histiocytoma (ANFH), spindle cell haemangioma, nodular Kaposi sarcoma, and angiosarcoma. Angiomatous fibrous histiocytoma tends to occur on the extremities of younger patients, can be associated with systemic symptoms and develops in deeper subcutaneous tissue, muscle or periosteum.[39] It is composed of monomorphic cells surrounded by prominent inflammatory cell infiltrate, with the occasional formation of reactive germinal centres. By immunohistochemistry, tumour cells in ANFH show desmin positivity.[40] Spindle cell haemangioma is a benign and frequently multifocal tumour showing a predilection for the distal extremities of young adults.[41,42] It is composed of thin-walled cavernous channels lined by flattened endothelial cells. Cavernous vessels are admixed with bland spindle cells, which characteristically contain round to more epithelioid cells, forming vacuoles or intracytoplasmic lumina.[41] Nodular Kaposi sarcoma shows a proliferation of CD34+ spindle cells, forming slit-like spaces containing erythrocytes.[43] In addition, lesional cells show consistent human herpes virus 8 nuclear positivity.[44,45] Cutaneous angiosarcoma usually develops on the face and scalp of elderly patients.[46] On histology, in addition to more solid areas, dissecting vascular channels are seen, which are lined by atypical cells with frequent mitoses, including atypical ones. Multilayering of tumour cells in angiosarcomas is a helpful diagnostic feature, as is consistently positive immunoreactivity for different vascular markers, such as CD31 and FLI-1.

Cellular benign fibrous histiocytoma

Cellular benign fibrous histiocytoma (CBFH) is a distinctive variant of fibrous histiocytoma, described as an entity by Calonje *et al.* in 1994,[47] and represents about 5% of cutaneous benign fibrous histiocytomas.[5] Lesions with a similar morphology were reported in the past as benign fibrous histiocytoma with a potential for local recurrence,[48] dermatofibroma extending into the

subcutis[49] and as an atypical fibrous histiocytoma (AtFH).[50] Importantly, the latter, due to its name, can cause confusion and should not be mistaken for an atypical ('pseudosarcomatous') fibrous histiocytoma, a variant of fibrous histiocytoma characterized by extreme focal cellular atypia (see below). In contrast to common fibrous histiocytoma, CBFH is usually not recognized clinically and has a recurrence rate as high as 26%, especially after incomplete excision.[5,47] It is important to highlight that the recurrence rates of all the variants of fibrous histiocytoma have been reported in series from referral cases. This means that the reported rates introduce a bias, which results in an overestimate of the recurrence rates.

CLINICAL FEATURES

CBFH presents in young to middle-aged adults (mean age 33 years) as a slowly growing solitary nodule on an upper limb/limb girdle (34%), followed by lower limb/limb girdle (27%), head and neck (20%) and trunk (12%), measuring from 5 to 25 mm.[47] Furthermore, it has the propensity to develop at unusual sites, such as the face, ears, hands and feet. The tumour shows male predominance (M:F = 1.9:1). The preoperative duration of the lesion is usually variable, from 2 weeks to 2 years.

HISTOLOGICAL FEATURES

Low-power magnification of CBFH shows either polypoid and circumscribed or non-exophytic and more infiltrative cellular proliferation, extending into the deep reticular dermis. A focal, lace-like extension or more fascicular growth, mainly along the septa into the superficial subcutis (Figure 6A), is present in about one-third of cases. Multinodular growth is rare. Defining histological features of CBFH are high cellularity, and a short fascicular as well as focal storiform growth pattern (Figure 6B).[47] Lesional cells have tapering nuclei with small eosinophilic nucleoli and relatively abundant, ill-defined, pale eosinophilic cytoplasm. Although a spindle cell morphology generally predominates, foci of more epithelioid cells can also occasionally be found. Normal mitoses are common and may number up to 10 mitoses/10 HPF (Figure 7A). Atypical mitoses are not seen. Areas of central necrosis or infarction may be found in up to 12% of tumours, while surface ulceration is less frequent (Figure 7B).[47] A consistent finding in all CBFH is areas of ordinary fibrous histiocytoma with hyalinized collagen bundles surrounded by lymphocytes, plasma cells, foamy macrophages, giant cells

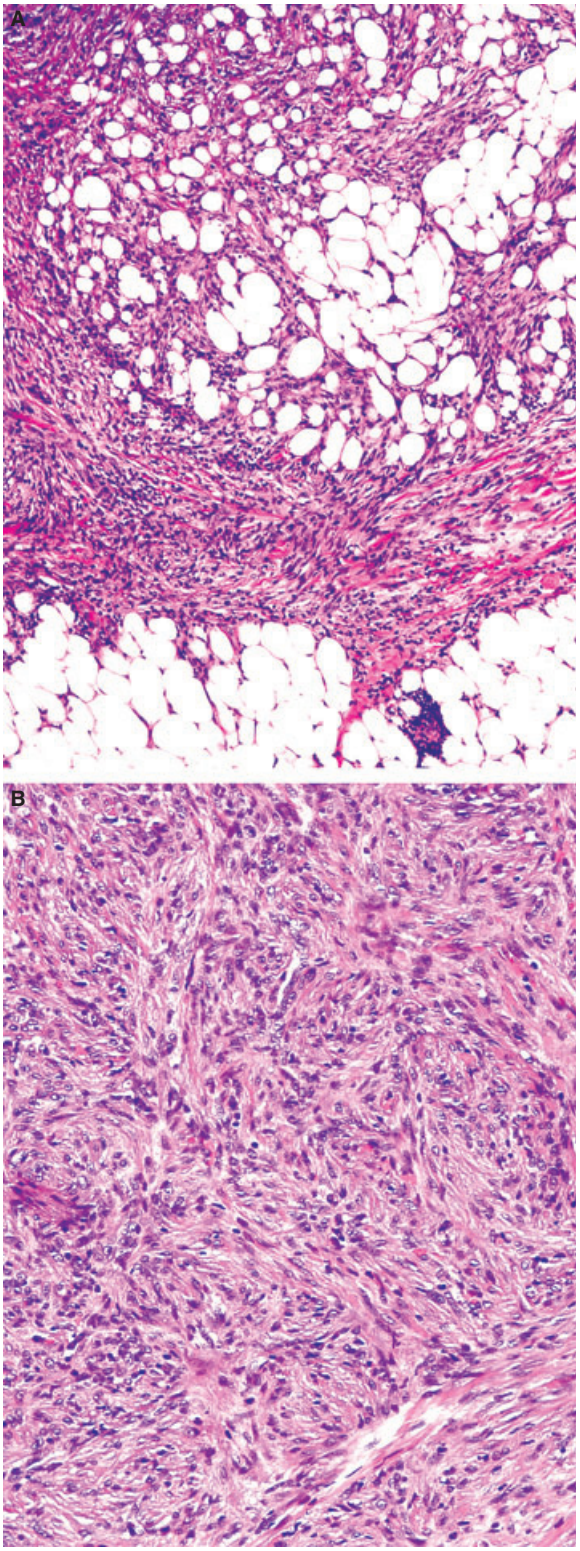

Figure 6. Cellular benign fibrous histiocytoma showing lace-like extension into superficial fatty tissue (**A**). High cellularity with short fascicular and storiform growth are defining histological features of a cellular benign fibrous histiocytoma (**B**).

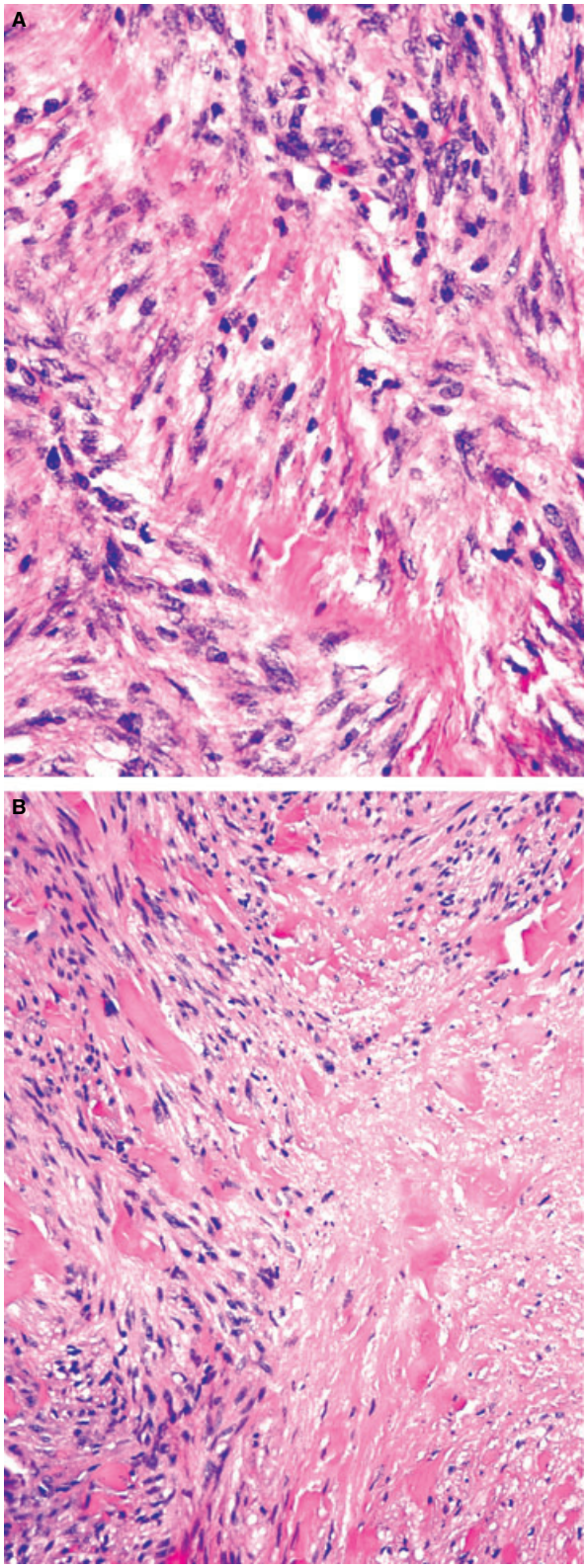

Figure 7. Cellular benign fibrous histiocytoma. While normal mitoses are common (**A**), atypical mitoses are not acceptable. Focal areas of necrosis are not unusual in cellular benign fibrous histiocytoma (**B**).

and areas of haemorrhage with haemosiderin deposition. Such features are mostly seen at the periphery of cellular areas, and are not as prominent as in common fibrous histiocytomas. Several types of fibrous histiocytoma may co-exist within the same lesion, and failure to recognize this may result in pitfalls in diagnosis.

By immunohistochemistry, CBFH shows variable focal SMA positivity in up to 60% of cases.[47] Rarely, large areas of the tumour are positive for this marker. SMA positivity coupled with variable positivity for calponin and rare focal positivity for H-caldesmon support a myofibroblastic line of differentiation. Focal CD34 positivity may be present, especially at the periphery of cellular areas (Figure 8), but is never diffuse. It is likely that this positivity is not really in the tumour cells but in peripheral normal stromal cells blending with the tumour. It must be stressed, however, that occasionally focal genuine positivity for CD34 may be seen in tumour cells. Exceptionally, very focal desmin positivity may be seen. Immunoreactivity for cytokeratins, EMA and S100 is negative. Factor XIIIa usually reveals a number of non-neoplastic tumour cells in the background.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis includes dermatofibrosarcoma protuberans and leiomyosarcoma. Dermatofibrosarcoma protuberans shows extensive replacement of the subcutis, diffuse CD34 positivity and cytogenetic

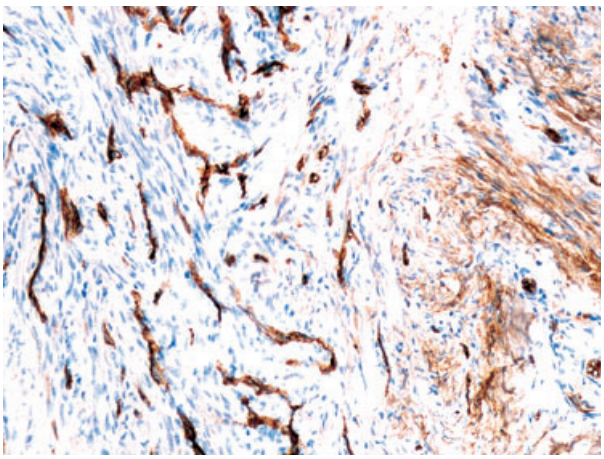

Figure 8. Cellular benign fibrous histiocytomas frequently show focal CD34 positivity, especially at the periphery of the lesions. This is a useful feature to distinguish the lesion from dermatofibrosarcoma protuberans, which shows diffuse CD34 positivity.

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evidence of the t(17;22) translocation.[51] Leiomyosarcoma displays plump eosinophilic spindle cells with cigar-shaped nuclei, more uniform fascicular growth and more diffuse SMA and desmin positivity in tumour cells.

Atypical fibrous histiocytoma

The term atypical (pseudosarcomatous) cutaneous histiocytoma was introduced in 1983 by Fukamizu *et al.*[52] Different names have been used since for histologically similar lesions: atypical cutaneous fibrous histiocytoma,[53] dermatofibroma with monster cells,[54] and atypical (pseudosarcomatous) benign fibrous histiocytoma.[55] The entity is currently known as an atypical fibrous histiocytoma (AtFH).[56] Although initial reports suggested a uniformly benign clinical course, with a low recurrence rate comparable to that of ordinary fibrous histiocytoma,[52–55] the largest published series of 59 AtFHs, by Kaddu *et al.*,[56] revealed a local recurrence rate of 14% following incomplete excision (three of 21 patients) and distant metastases in two patients (9.5%), of whom one died due to the disseminated disease 96 months after initial resection. No histological features were found to be predictive for local recurrence or development of metastatic disease.[56]

CLINICAL FEATURES

AtFH most commonly develops in young to middle-aged adults in the fourth to fifth decade of life (mean age about 40 years). It generally presents as a non-painful solitary polypoid, nodular or slightly raised lesion, measuring from 3 to 80 mm (median about 15 mm) most commonly on the lower limb/girdle (44%), followed by the upper limb/girdle (32%) and trunk (11%), with a few cases reported in the head and neck and genital region.[52–56] There is a roughly equal gender distribution.

HISTOLOGICAL FEATURES

Essential histological features in AtFH are scattered pleomorphic histiocyte-like and spindled fibroblast/myofibroblast-like cells admixed with multinucleated giant cells in the background of a common fibrous histiocytoma. Pleomorphic cells have hyperchromatic, large and irregularly shaped nuclei with small but prominent nucleoli and often abundant eosinophilic or foamy cytoplasm with indistinct borders (Figure 9). On average, three mitoses/10 HPF are usually present, with occasional atypical mitoses. Pleomorphism can be focal (<25% of the tumour) and mild or more widespread and pronounced. Additional histological features found infrequently in AtFH are areas of geographic necrosis and infiltrative growth into the subcutis.

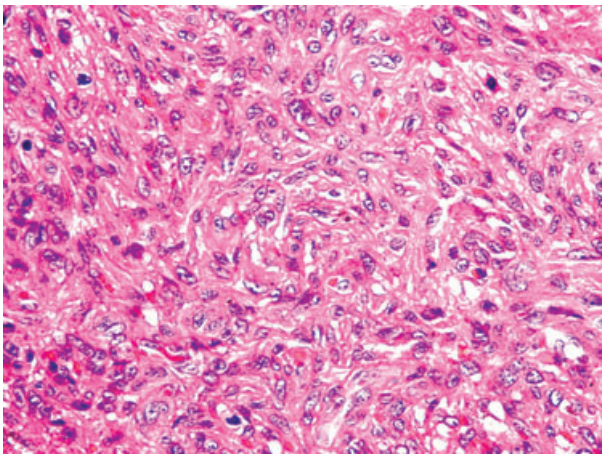

Figure 9. Atypical fibrous histiocytoma showing more pleomorphic cells with irregular vesicular nuclei, prominent nucleoli and frequent mitoses.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of AtFH includes atypical fibroxanthoma (AFX) and its potential mimics, such as squamous cell carcinoma (SCC) and melanoma. AFX generally presents as a rapidly growing polypoid and ulcerated lesion on sun-damaged skin in elderly patients, mostly in the head and neck region. Histologically prominent solar elastosis is a requisite and the tumour shows sheets of histiocyte-like, spindle-shaped and multinucleated cells with prominent pleomorphism throughout the lesion and brisk mitotic activity, including atypical mitoses. Associated features of a common fibrous histiocytoma, a constant feature in AtFH, are not seen in AFX. SCC and melanoma can be excluded by associated epidermal changes and by using appropriate immunohistochemical stains (cytokeratins, S100).

Angiomatoid fibrous histiocytoma

ANFH was reported in 1979 by Enzinger in a series of 41 cases, as a variant of malignant fibrous histiocytoma (MFH) (angiomatoid MFH), which showed a predilection for extremities and occurred at a much younger age than other subtypes of MFH.[57] Subsequent larger studies have confirmed

that it also differs in biological behaviour, having a much more favourable prognosis and benign clinical course in the majority of patients.[39,58,59] Unfortunately, the newer name is confusing, as this tumour is not a variant of fibrous histiocytoma and has no relation whatsoever with aneurysmal fibrous histiocytoma. ANFH has therefore been recognized as a distinct clinicopathological entity, rather than a subtype of MFH, by the recent World Health Organization (WHO) classification of the tumours of soft tissue.[60] The term 'malignant' has been omitted from its name, and the tumour has been placed in the category of tumours with intermediate malignancy.[60] Cytogenetic and molecular genetic studies have discovered reproducible genetic abnormalities in ANFH: *EWSR1–CREB1* fusion gene resulting from t(2;22)(q34;q12),[61,62] *FUS–ATF1* fusion gene resulting from t(12;16)(q13;p11),[63,64] and *EWSR1–ATF1* fusion gene resulting from t(12;22)(q13;q12),[65,66] in decreasing order of frequency. Demonstration of these translocations is a very useful diagnostic adjunct in correctly recognizing ANFH. Interestingly, the first and third cytogenetic abnormalities are found in clear cell sarcoma (melanoma of soft parts) not only of soft tissue but also of the gastrointestinal tract.

CLINICAL FEATURES

ANFH represents <1% of all soft tissue tumours.[60] It occurs over a broad age distribution, ranging from 2 months to 71 years, with a median age of 13 years in one review,[57] and a mean age of 17 or 20 years, respectively, in two other reviews,[39,59] but it generally develops in children or young adults.[39,57,59] Predilection sites are the extremities, followed by trunk and head and neck.[39,57,59] About two-thirds of tumours develop in areas where normal lymphoid tissue is found, such as antecubital fossa, axilla, inguinal area, popliteal fossa, supraclavicular area, and posterior/anterior neck.[59] A minority of patients have associated systemic symptoms, such as fever, malaise, anaemia, weight loss, and polyclonal gammopathy, which disappear on excision of the tumour. ANFH presents as a slow-growing, well-circumscribed and partly encapsulated multi-nodular tumour measuring 20–40 mm in the largest dimensions.[39,57,59] The tumour in usually located in the subcutis, but may infiltrate into the dermis and/or into underlying muscle or even periosteum. Predictors of local recurrence are incomplete/marginal excision, irregular border of the tumour and location in the head and neck area.[39] The two largest studies of ANFH showed local metastases to be present in up to 4% of cases, which were managed successfully by local excision,[39,59] and the presence of distant metastases resulting in the death of a single patient in a total of 180 patients.[39,59] Importantly, no correlation has been established between any of the histological parameters and the development of regional or distant metastases.[39]

HISTOLOGICAL FEATURES

ANFH is characterized by sheets or short fascicles of round to spindle-shaped cells forming nodule(s), multifocal areas of haemorrhage within nodules with the formation of large, blood-filled spaces, lymphoplasmacytic infiltrate and usually an incomplete fibrous pseudocapsule (Figure 10A). In individual lesions, either more rounded or more spindle cells can predominate,[59] and the proportion of other components may also vary greatly among different tumours. The rounded cells have uniform vesicular nuclei, infrequent mitoses and their cytoplasm is minimal (Figure 10B). Areas with predominantly rounded cells are generally more cellular, while spindle cells usually display a slightly greater degree of nuclear polymorphism. Tumours with variable cytological atypia, which may be prominent, are rarely encountered. The biological behaviour does not correlate with the histological grade. Focal myxoid degeneration of the stroma can be present. Haemorrhagic areas may be accompanied by haemosiderin deposition, accumulation of siderophages and occasional giant cell formation. The lymphoplasmacytic infiltrate is usually seen surrounding tumour nodules, may be sparse or quite prominent, with the formation of randomly distributed germinal centres. A fibrous pseudocapsule, surrounding the tumour, may be prominent and thick. Together with the lymphoplasmacytic infiltrate and formation of germinal centres, the fibrous pseudocapsule may give the false impression of a lymph node.

By immunohistochemistry, the lesional cells show strong cytoplasmic desmin positivity (Figure 11) in about 50–80% of cases.[40,59] In addition, scattered desmin-positive cells can also be demonstrated dispersed within the lymphoplasmacytic infiltrate surrounding the tumour. Staining for α-SMA, HHF35 and calponin has given inconsistent results, with 0–33% positivity. Expression of CD68, CD99 and EMA has also been observed in varying proportions, although these markers lack specificity. All tumours are consistently negative for low- and high-molecular-weight cytokeratins, S100, CD31, myoD1, myogenin and myoglobin.[59,67]

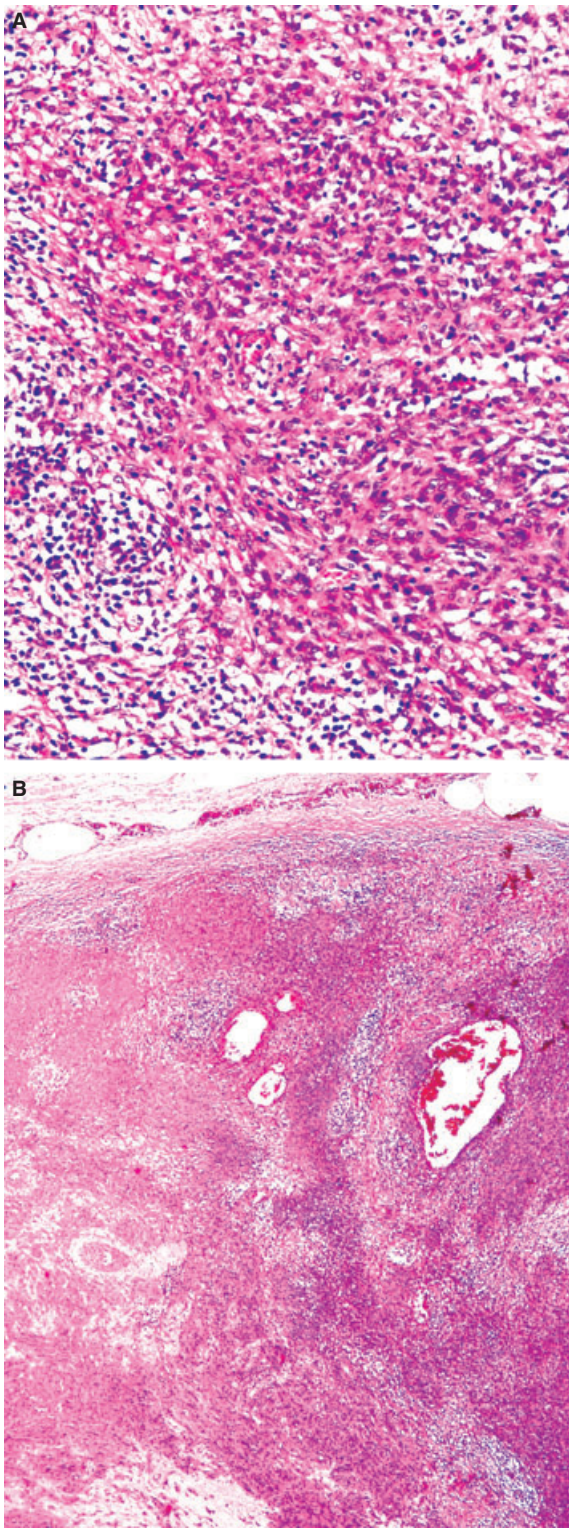

Figure 10. Angiomatoid fibrous histiocytoma is composed of nodules, blood-filled spaces, inflammation and an incomplete fibrous pseudocapsule (**A**). This nodule is composed of epithelioid and short spindle cells, surrounded and infiltrated by mononuclear cells, mostly lymphocytes and plasma cells (**B**).

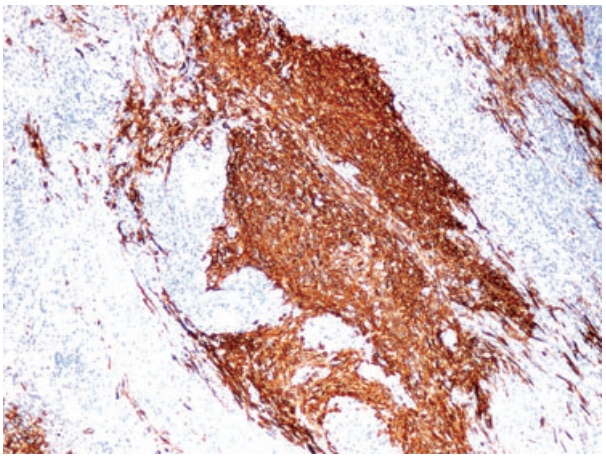

Figure 11. Angiomatoid fibrous histiocytoma. Lesional cells show strong desmin positivity.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis includes a lymph node with possible neoplastic growth, including metastasizing fibrous histiocytoma. Closer examination fails to demonstrate the characteristic architecture of a lymph node, with well-formed subcapsular and medullary sinuses and regular arrangement of germinal centres. AFH is located in the dermis, and contains, in addition to slit-like or cavernous haemangioma-like pseudovascular spaces, also histological features of a common fibrous histiocytoma, usually at the periphery of the lesion. Due to the epithelioid morphology of ANFH, such as diffuse desmin positivity, rhabdomyosarcoma might enter into its differential diagnosis. However, other markers of skeletal muscle differentiation, such as myoglobin, myoD1 and myogenin, are consistently negative in ANFH.

Plexiform fibrous histiocytoma (plexiform fibrohistiocytic tumour)

Plexiform fibrohistiocytic tumour was reported in 1988 by Enzinger and Zhang[68] in a series of 65 cases, as a distinctive tumour with features reminiscent of both fibrous histiocytoma and fibromatosis. Although initially thought to be of fibrohistiocytic origin, its exact histogenesis is not known. Nevertheless, mounting evidence since its original description suggests a myofibroblastic line of differentiation.[69] Until the issue is resolved, plexiform fibrohistiocytic tumour has been retained under the group of fibrohistiocytic neoplasms, and is thus also discussed in the present review. The unfortunate term plexiform fibrous histiocytoma (PFH)

was adopted by WHO, and is confusing, since the tumour is not part of the spectrum of fibrous histiocytoma.

CLINICAL FEATURES

PFH usually presents as a slowly growing non-painful nodule, or less frequently as an indurated flat plaque preferentially on the upper extremities (50%), followed by the lower extremities (20%), trunk (15%) and head and neck region (10%).[68–73] A single case of intra-osseous occurrence of a PFH within the proximal epiphysis of the tibia has also been described.[74] Although a PFH may develop at any age, the tumour occurs most frequently in children and adolescents, with about 70% of patients being <20 years old.[68–73] A minority of cases have been found to be of congenital origin.[69,72] Initial reports suggested a striking female predominance.[58,70,71] Nevertheless, reviewing all published cases in the English literature, the difference was not that prominent and we have estimated) a female:male ratio of about 1.5:1. PFH rarely exceeds 30 mm in diameter,[68] but giant lesions measuring up to 80 mm have also been reported.[75]

Although the biological potential of PFH is at present not possible to predict, the prognosis is generally favourable. Local recurrences are common, and may even be multifocal.[58] The reported recurrence rate varies from 12.5 to 50%.[68,69,71] Spontaneous regression of a recurrent lesion after 20 years has been reported in an exceptional case.[69] Locoregional lymph-node metastases have been reported in two patients by Enzinger and Zhang,[68] and in one patient by Remstein *et al.*[71] Systemic metastases to the lungs have been confirmed by histological examination in three patients, and were suspected in an additional patient.[71,76] Despite the presence of lung metastases, the overall outcome was relatively favourable, resulting in a fatal outcome in a single patient.[76] There are, at present, unfortunately no reliable histological parameters in PFH that would predict the risk of local recurrence, regional lymph node or development of systemic metastases. Cytogenetic analysis has so far been performed on two cases of PFH.[77,78] No consistent chromosomal anomaly has yet been demonstrated; one case revealed a complex karyotype with numerous deletions[78] and the other a simpler karyotype of 46,XY,t(4;15)(q21;q15).[77]

HISTOLOGICAL FEATURES

PFH is a poorly circumscribed proliferation located in the subcutis, with possible extension into the dermis, skeletal muscle or both. Pure intradermal lesions, which tend to be better delineated, have also been described.[70] It is composed of two main components, albeit in variable proportions: histiocyte-like and spindled fibroblast-like cells. Mononuclear histiocyte-like cells have pale cytoplasm, round to oval, centrally located nucleus with one to three small nucleoli, and tend to aggregate and form nodules. Nodules frequently contain also multinucleated osteoclast-like giant cells and transitional binucleate cells (Figure 12A). Fibroblast-like spindle cells have pale cytoplasm, slender tapered nuclei with inconspicuous nucleoli, and form intersecting bundles or fascicles (Figure 12B). They can frequently be seen at the periphery of the nodules, interconnecting adjacent nodules. Both components, histiocyte-like and spindled fibroblast-like, give the lesion a characteristic plexiform and (multi)nodular arrangement. Little cellular pleomorphism is generally present, and mitotic activity is low, with a mean number of three mitoses/10 HPF.[71] Although cases with more pronounced cellular atypia, pleomorphism, atypical mitoses and intravascular growth can occasionally be seen, their biological significance is not clear.[68,71,73] An atypical variant of PFH displaying significant cytological atypia and pleomorphism has been reported in a 13-year-old boy, with unremarkable follow-up of 2 years.[79] Additional histological features that may be found in these lesions are foci of haemorrhage, haemosiderin deposition, chronic inflammatory cells, myxoid degeneration, stromal hyalinization and metaplastic bone formation.[68–70,73,80]

Three distinct growth patterns can be observed on the basis of the proportions of each component: fibrohistiocytic, fibroblastic and mixed. While predominantly fibrohistiocytic variants tend to be better circumscribed, predominantly fibroblastic variants appear more infiltrative and less delineated.[71] Interestingly, a storiform growth pattern is not a feature of PFH,[68] and, when present, an alternative diagnosis should be considered.

By immunohistochemistry, histiocyte-like cells and osteoclast-like giant cells of PFH display CD68 positivity, while fibroblast-like cells frequently show at least focal positivity for SMA.[69] Some of the mononuclear cells within the nodules can also show focal SMA positivity. Tumour cells are consistently negative for cytokeratins, desmin, S100 and CD34.[73]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of PFH includes other lesions with a plexiform growth pattern, such as fibrous hamartoma of infancy, plexiform spindle cell (melanocytic) naevus, plexiform neurofibroma, and also fibromatosis, soft

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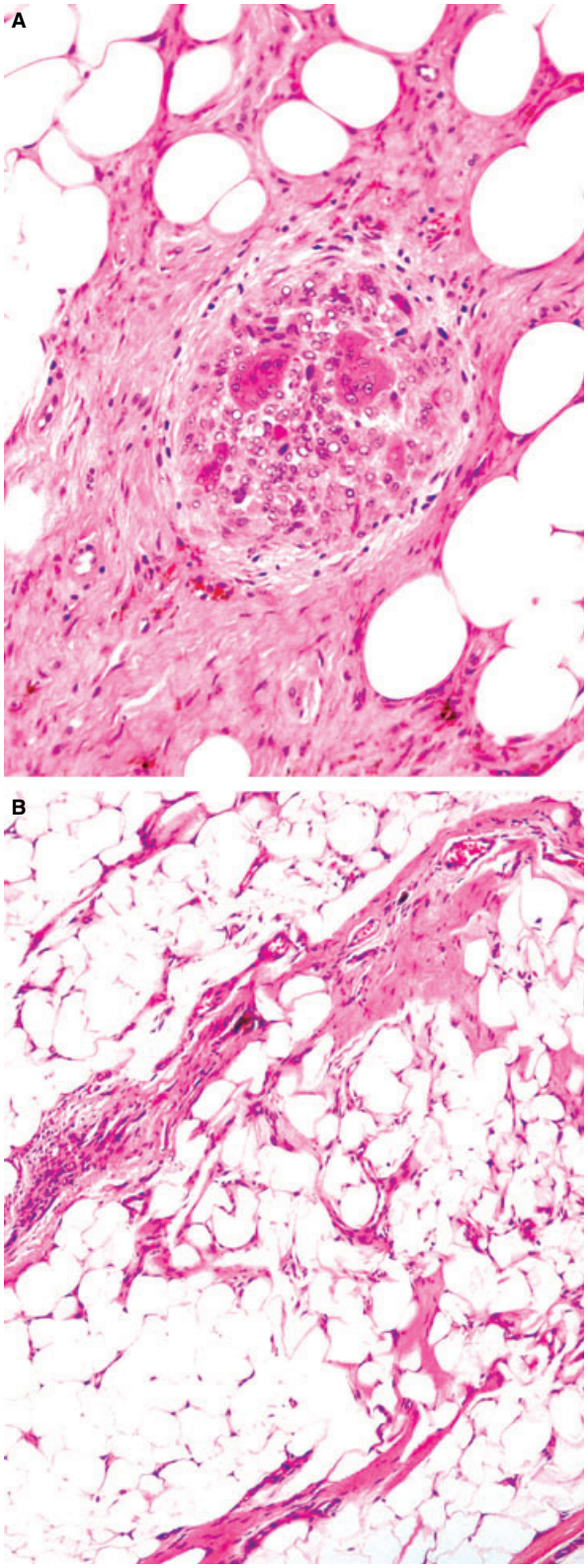

Figure 12. Plexiform fibrous histiocytoma is composed of two main components: histiocyte-like (**A**) and spindled fibroblast-like cells (**B**). Either of the two component can predominate.

tissue giant cell tumour and cellular neurothekeoma. Fibrous hamartoma of infancy is exceedingly rare beyond the age of 2 years.[81] It is composed of dense fibroblastic trabeculae, primitive mesenchymal cells embedded in a myxoid matrix and mature fat. Multinucleated giant cells are not a feature in fibrous hamartoma of infancy. Plexiform spindle cell naevus, a variant of blue naevus, can be properly recognized by the presence of melanin in the cytoplasm of tumour cells and by strong S100 positivity. Plexiform neurofibroma shows tortuous masses of expanded nerve branches in a neurofibromatous background. S100 protein positivity in plexiform neurofibroma is usually not as prominent and as diffuse as in melanocytic lesions or schwannomas. Distinction between a fibroblastic variant of PFH and fibromatosis (extra-abdominal desmoid) can be challenging. Nevertheless, serial sections and sampling of the lesion will usually demonstrate small foci of histiocyte-like cells and multinucleated giant cells, characteristic of PFH. Such foci, in addition to a plexiform growth pattern in the subcutis, should enable correct recognition of the lesion. Soft tissue giant cell tumour generally occurs in older patients and does not display a plexiform growth pattern. Cellular neurothekeoma is a poorly circumscribed lesion, usually located within the dermis. It is composed of nests and fascicles of epithelioid and spindle cells with eosinophilic cytoplasm and vesicular nuclei. Multinucleated giant cells can occasionally be seen. By immunohistochemistry, cellular neurothekeoma almost always shows diffuse positivity for NKIC3, focal positivity for PGP 9.5 and focal smooth muscle positivity in up to half of cases. S100 staining is consistently negative. Cellular neurothekeoma and PFH display some histological similarities and, based on this, a common histogenesis has thus been proposed for these two lesions.[82,83] We do not believe that the entities are related.

Atypical fibroxanthoma

The term atypical fibroxanthoma (AFX) was introduced in 1961 by Helwig[84], reporting a series of 20 elderly patients with a solitary tumour on sun-exposed skin. The lesions were composed of 'bizarre' cells displaying a xanthomatous appearance and, despite marked cellular atypia, followed a benign clinical course.[84] With the introduction of new techniques, especially immunohistochemistry, it has become apparent that many cases reported in the past as AFXs, especially those with metastases, probably represented other high-grade sarcomas or non-mesenchymal malignancies.[5] Furthermore, tumours with a similar morphology reported in young adults on non-sun-exposed skin probably

represented examples of AtFH.[85] The following strict histological criteria, supplemented by a panel of immunohistochemical antibodies, is therefore of paramount importance for correctly recognizing AFX, which is regarded as a diagnosis of exclusion (see below). The treatment of AFX consists of complete local excision and is usually curative. Recurrences following complete excision are relatively rare and distant metastases are exceptional.[86] Ultraviolet (UV) light-induced *p53* gene mutations occurring at dipyrimidine site(s) have been constantly demonstrated in AFX, suggesting a pivotal role of UV radiation in its pathogenesis.[87,88]

CLINICAL FEATURES

AFX generally presents as a solitary, rapidly growing polypoid lesion or nodule, frequently ulcerated on sun-exposed skin of the head and neck area.[85,89] It is characteristically a tumour of elderly patients, occurring in the eighth decade of life (mean age 77 years) and shows male predominance.[90]

HISTOLOGICAL FEATURES

Conventional AFX is composed histologically of an admixture of highly pleomorphic spindle, epithelioid (histiocyte-like) and multinucleated giant cells in the dermis (Figure 13A). Mitoses are frequent and also include atypical forms. Surface ulceration precludes adequate evaluation of epidermal changes, e.g. the presence of epidermal dysplasia or melanocytic proliferation. An epidermal collarette at the periphery of the lesion is frequently observed and may extend along the base of the lesion. Skin adnexa are generally surrounded but not destroyed by the tumour. A very limited extension into the superficial subcutis may be present.[90] The deep margin is generally pushing rather than infiltrative. The proportion of individual cell types within individual lesions may vary, from predominantly spindle to predominantly epithelioid (histiocyte-like) lesions. A spindle cell non-pleomorphic variant of AFX is characterized by fascicles of monomorphic spindle cells with eosinophilic cytoplasm within the dermis, frequent mitotic activity and lack of the pleomorphism of a conventional AFX (Figure 13B).[91] This variant, due to its bland morphology, is frequently not properly recognized. Several additional morphological changes have been described in AFX, either focally or more diffusely. They include pseudoangiomatous areas, granular cell change, clear cell change, osteoclast-like giant cells, intracellular deposition of haemosiderin (a so-called 'pigmented variant'), myxoid degeneration, keloid-like areas, prominent sclerosis and regression.[92–111] The

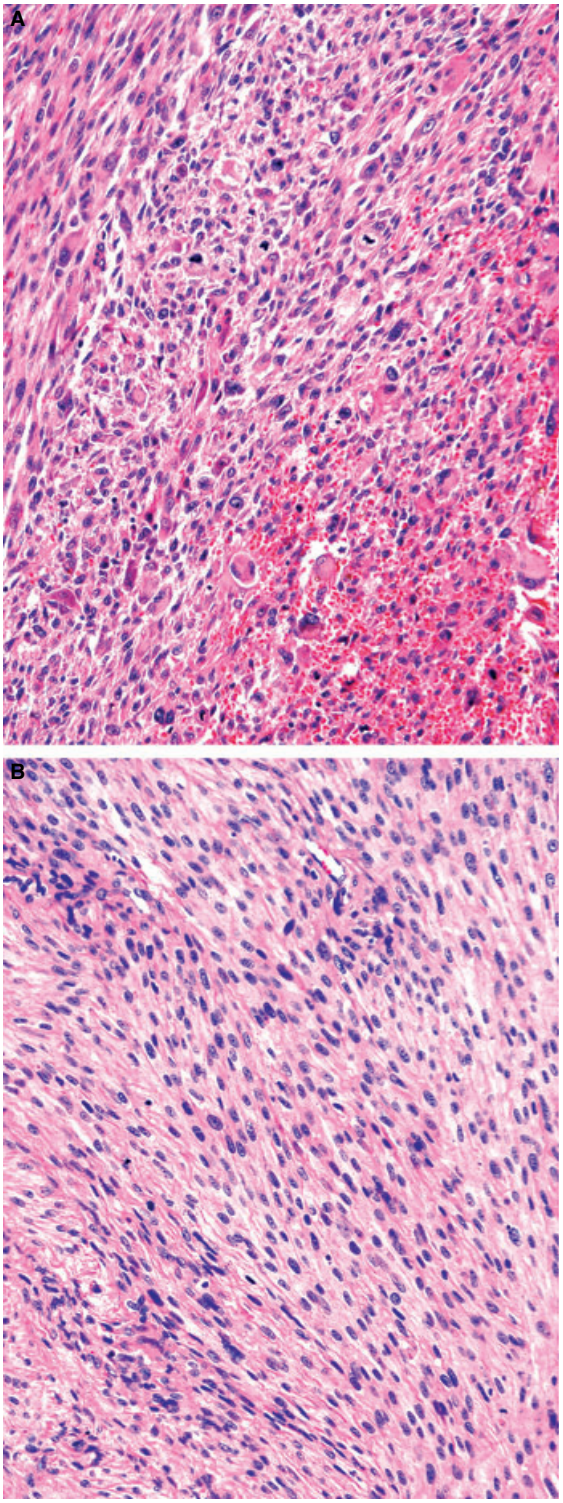

Figure 13. Atypical fibroxanthoma is composed of an admixture of highly pleomorphic epithelioid (histiocyte-like), spindle and multinucleated giant cells with frequent mitoses including atypical ones (**A**). Spindle cell non-pleomorphic variant is characterized by fascicles of monomorphic cells with eosinophilic cytoplasm and frequent mitoses (**B**).

formation of osteoid[112] and chondroid matrix[105] has also been reported, but this finding is exceptional.

Histological features not acceptable for the diagnosis of an AFX are perineural/intraneural invasion, vascular invasion, prominent infiltration of the subcutis or beyond, as well as areas of intratumoral necrosis. Such lesions are in the absence of particular line of differentiation (see differential diagnosis) better classified as dermal sarcomas (not otherwise specified) to highlight probably aggressive behaviour.

IMMUNOHISTOCHEMISTRY

At present, no single reliable immunohistochemical marker has been detected to confirm the diagnosis of AFX, which still remains a diagnosis of exclusion. A panel of antibodies is therefore mandatory to exclude its potential mimics (see below). By definition, AFXs are consistently negative for various low- and high-molecular-weight cytokeratins, S100 and desmin. Reactive S100+ dendritic cells are frequently seen dispersed among the lesional cells. Focal smooth muscle positivity can be detected in as many as 45% of AFXs,[90,113] while focal EMA positivity in the absence of cytokeratin positivity has been reported to be present in 24%.[90] Focal cytoplasmic positivity for CD31 has been observed in the more epithelioid (histiocyte-like) areas of AFX in 10% of cases, which expands the spectrum of CD31+ histiocytic lesions.[90] Although diffuse and strong CD10 and CD99 positivity has been described in AFXs, these markers are non-specific and non-contributory in the diagnosis of AFX.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of AFX includes spindle cell SCC, spindle cell melanoma and leiomyosarcoma. Consistent cytokeratin, S100 and desmin reaction by immunohistochemistry in AFX should allow its proper recognition.

Metastasizing fibrous histiocytoma

Over the years, it has become apparent that fibrous histiocytomas exceptionally give rise to locoregional and systemic metastases. A total of 12 metastasizing fibrous histiocytomas have been reported by August 2009.[114–120]

CLINICAL FEATURES

The primary lesion was most often located on extremities (four cases, 33%), followed by back (three cases, 25%), neck (two cases, 17%) and scalp in a single case. The primary lesions measured from 4 to 50 mm. There is a male predominance (2.6:1). At the time of metastases, patents were from 3 to 65 years of age (mean about 30 years). The time between excision of the primary lesion and development of metastases was from 2 to 157 months. Metastases were preceded by one or more local recurrences in 67% (8/12). The sites of metastases were loco-regional lymph nodes (5/12), lungs (4/12), or both (3/12). In one patient, multiple skin and colon metastases were present, in addition to loco-regional and lung metastases.[56] While the clinical course was indolent in the majority of patients with metastasizing dermatofibroma, one patient died of disseminated disease.[56]

HISTOLOGICAL FEATURES

Primary lesions were most often cellular fibrous histiocytomas (6/12), followed by ordinary fibrous histiocytomas (3/12), and a single case each of combined aneurysmal/atypical (pseudosarcomatous) and atypical (pseudosarcomatous) fibrous histiocytoma. Metastases showed either a similar morphology to the primary lesion (7/12), or were angiomatoid (3/12) or more cellular fibrous histiocytomas. At present, there are no histological features in fibrous histiocytomas that would reliably predict the risk of loco-regional and/or distant metastases.

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