Aneurysmal and haemangiopericytoma-like fibrous histiocyoma

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Abstract

Aim—To describe the clinicopathological features of 33 aneurysmal fibrous histiocyomas (AFH), including five cases with a haemangiopericytoma-like pattern.

Methods—Thirty three cases of AFH were studied by using routine histology and immunohistochemistry for factor XIIIa, the "cell activity marker" E9 (anti-metallothionein), NK1C3 (CD57), smooth muscle actin (SMA), factor VIII, ulex europaeus agglutinin, JC70A (CD31), and QBEND10 (CD34). The time dependent variation in histopathological features was evaluated by statistical methods (Pearson χ^2 , likelihood ratio χ^2).

Results—Of the AFHs, 29 of 33 occurred on the extremities of adults (age range 30 to 50 years), six of which were associated with rapid growth, probably caused by trauma, and pain. Twenty one lesions were thought to be vascular and/or melanocytic lesions, including two melanomas, because of a bluish-black and/or cystic appearance. Histologically, large areas of haemorrhage, up to 50% of the tumour bulk, lacking an endothelial lining were seen in otherwise typical fibrous histiocyomas. Five cases resembled nodular stages of Kaposi's sarcoma. Variable haemosiderin deposition in histiocytes (18/33) and giant cells (11/33) was suggestive of haemosiderotic histiocyoma. A haemangiopericytoma-like pattern was seen in five otherwise indistinguishable cases. On immunohistochemistry, variable reactivity was seen for factor XIIIa (18/30), with E9 (18/30), NK1C3 (19/30), and for SMA (14/30), but labelling for vascular markers was not detected. Early lesions without iron deposition were factor XIIIa positive; late lesions with iron deposition were factor XIIIa negative. Labelling for SMA correlated with prominent sclerosis.

Conclusion—AFHs, including a haemangiopericytoma-like variant, have a characteristic time dependent histological and immunophenotypic profile, clearly different from nodular type Kaposi's sarcoma.

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Keywords: dermatopathology, immunohistochemistry, aneurysmal and haemangiopericytoma-like fibrous histiocyoma, dermatofibroma, fibrohistiocytic lesion, haemangiopericytoma.

Aneurysmal fibrous histiocyoma (AFH) is an unusual type of fibrohistiocytic tissue response

characterised by noticeable erythrocyte extravasation. AFHs are often mistakenly diagnosed as melanocytic or vascular lesions. Since the first report by Santa Cruz and Kyriakos¹ in 1981 the AIDS pandemic has raised awareness of Kaposi's sarcoma. As AFH may sometimes closely mimic nodular lesions of Kaposi's sarcoma histologically,² it is important that the differences between these lesions are highlighted.

The present study (1) describes a new, as yet unrecognised, haemangiopericytoma-like pattern in five of 33 cases of AFH; (2) elaborates distinct criteria to differentiate AFH from nodular types of Kaposi's sarcoma; and (3) documents a time dependant variation in the histopathological features of AFHs, thereby underlining their reactive character.

Methods

Thirty three cases of AFH, routinely fixed in formalin and embedded in paraffin wax, were retrieved from the files of the Dermatohistopathological Laboratory (15 000 skin specimens/year) of the Department of Dermatology, University of Innsbruck, Austria.^{3,4} Basic clinical details (table 1) were obtained from histopathological request forms and patients' notes; follow up data were available for 28 of the 33 patients, either from medical records or from personal contact with the patients themselves or their general practitioner.

Routine staining procedures (haematoxylin and eosin, Perls' prussian blue stain for iron, melanin, van Gieson, and trichrome stains) and immunohistochemical labelling (table 2) were carried out as described previously.³⁻⁶

Specimens were analysed for the absence/presence of prominent sclerosis, defined as including the centre of the lesion, as well as for the absence/presence of iron with or without associated giant cells. Immunoreactivity was analysed independently by two observers (BWZ and BGZ). Only cells staining well above the background level (occasional faint labelling around strongly positive cells, most likely due to antigen diffusion) were regarded as positive. Generally, good correlation and reproducibility were achieved by the two observers.

STATISTICAL EVALUATION

Statistical analysis was carried out using the SYSTAT statistical package (Systat Inc., Evanston, Illinois, USA). The absence/presence of prominent sclerosis (1 DF), iron deposition with or without associated giant cells (2 DF)

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Table 1 Clinical data of aneurysmal (cases 1–28) and haemangiopericytoma-like (cases 29–33) (“angiomatoid”) fibrous histiocytoma

Case no.	Sex, age (years)	Localisation	Clinical (differential) diagnosis
1	F,41	Lower arm	? Angioma, blue naevus, malignant melanoma metastasis
2	F,34	?	Naevus
3	F,32	Upper arm	Dermatofibroma
4	F,31	Elbow	? Foreign body granuloma
5	F,73	Back	?
6	F,30	Thigh	? Histiocytoma with haemorrhage, blue naevus
7	M,36	Calf	Recurrence of dermatofibroma
8	M,34	Lower arm	Granuloma pyogenicum
9	M,?	Elbow	Dermatofibroma
10	M,50	Thigh	? Squamous/basal cell carcinoma
11	F,25	Calf	Blue tumour cutis
12	M,31	Knee	Blue naevus
13	M,38	Upper arm	Tumour cutis
14	M,9	Calf	Tumour cutis
15	F,44	Achilles tendon	? Histiocytoma, atypical fibroxanthoma
16	M,23	Thigh	Blue naevus
17	F,42	Buttock	? Histiocytoma, foreign body granuloma
18	M,56	Ankle	? Pyogenic granuloma
19	F,32	Upper arm	? Melanoma
20	F,44	Upper arm	? Angiokeratoma, thrombosed angioma
21	F,33	Knee	Tumour cutis
22	F,35	Trunk	Dermal naevus
23	M,43	Knee	Dermatofibroma
24	F,32	Shoulder	Blue naevus
25	M,42	Upper arm	Dermatofibroma
26	F,36	Thigh	? Haematoma, blue naevus, dermatofibroma
27	M,30	Upper arm	Dermatofibroma
28	M,42	Thigh	? Angioma
29	M,60	Knee	Dermatofibroma
30	F,53	Back	Traumatised histiocytoma
31	F,64	Back	? Scar, basal cell carcinoma
32	F,35	Fossa poplitea	? Lymphocytoma
33	F,24	Calf	Histiocytoma

Table 2 Details of the antibodies used for immunohistochemistry

Antibody or marker	Antibody type	Dilution	Source	Main specificity
Factor XIIIa	Polyclonal	1 in 50	Behring	(Papillary) dermal dendritic cells
E9	Monoclonal	1 in 10 000	Supernatant	Epidermal basal cell layer, peripheral adnexal epithelium
NK1/C3 (CD57)	Monoclonal	1 in 5	Monosan	Natural killer cells, mast cells
Smooth muscle actin	Monoclonal	1 in 50	Boehringer	Smooth muscle cells, myofibroblasts
Ulex europaeus agglutinin (biotinylated)	–	1 in 100	Vector	Endothelial cells
Factor VIII	Polyclonal	1 in 20	Dako	Endothelial cells
JC/70A (CD31)	Monoclonal	1 in 10	Dako	Endothelial cells
Q BEND 10 (CD34)	Monoclonal	1 in 50	Oxoid	Endothelial cells, dermal dendritic cells

Source: Behringwerke, Marburg, Germany; Monosan, Uden, Netherlands; Boehringer Mannheim GmbH, Germany; Vector Laboratories Inc., Burlingame, CA, USA; Dako, Glostrup, Denmark; (Oxoid) Unipath Ltd., Basingstoke, Hampshire, UK.

and labelling with anti-factor XIIIa, anti-metallothionein, anti-smooth muscle actin (SMA) and NK1C3 (1 DF) were tested in a multivariate analysis combining two parameters for diagnostic reliability. As in previous studies,^{7,8} a reaction was regarded as positive when more than 5% of the cells were stained. Pearson's χ^2 test and likelihood ratio χ^2 were also used for statistical analysis.⁹

Results

Clinically (table 1), AFH mainly occurred on the extremities (27/33) of adult females (38.5 ± 12.8 years; male:female ratio 3:4). Lesions measured 0.5 to 1 cm, were flat to exophytic with a brown to bluish-black colour and a firm, partially cystic consistency (fig 1). Histiocytoma was correctly diagnosed in less than one third of the patients (10/33); in the rest the clinical diagnosis included traumatised lesions with haemorrhage (five of 33), vascular (six of 33) or melanocytic lesions (10/33), and rarely lymphocytoma, squamous or basal cell carcinoma. In two cases (metastatic) malignant melanoma was suspected. According to the patients, lesions had been present between two

months and five years. Six patients mentioned a history of insect bite or trauma shortly before the lesion developed. For these lesions rapid growth and some moderate pain were reported. One case (case 7) was sent as a recurrence of

Figure 1 Clinical presentation of AFH. Note the exophytic lesion with slight scaling as well as irregular mixture of yellow-white to bluish-black and dark red colours mimicking a (nodular) malignant melanoma (case 19).

Figure 2 AFH with moderate haemangiopericytoma-like features. Note the endothelial lining of ectatic vessels as well as diffuse erythrocyte extravasation within the storiform pattern of spindle shaped cells similar to the nodular variants of Kaposi's sarcoma (case 33) (haematoxylin and eosin).

an "ordinary" dermatofibroma which had not been excised completely six months before. Most lesions were excised with clear margins (2–3 mm) and in cases of suspected malignant melanoma with wide margins (>5 mm). No recurrence was seen in the 28 cases after nearly 10 years of follow up (9.0 ± 4.3 years).

HISTOLOGY

Serial sections revealed identical findings. Scanning magnification revealed the typical appearances of dermatofibromas or fibrous histiocytomas: moderately well circumscribed dermal to subcutaneous lesions with epidermal hyperplasia, often with a moderate increase in basal pigmentation (nine of 33), occasional sebaceous differentiation (two of 33) or basal cell carcinoma-like features (one of 33); mainly peripheral sclerotic collagen (31/33), which was defined as prominent when central parts were also involved (18/33); and a moderate lymphohistiocytic infiltrate. A small grenz zone towards the epidermis and a smooth nodular

Figure 3 AFH with notable haemangiopericytoma-like features. Note the typical staghorn- or antler-like lumina lined by endothelial cells and focal giant cells (case 32) (haematoxylin and eosin).

border towards the subcutis, or, alternatively, superficial lace-like involvement of the subcutis beside short scalloped extensions along pre-existing septa were also present. In contrast to typical fibrohistiocytic lesions, AFH had bizarre, flash-like retraction artefacts which were partially expanded by large haemorrhagic zones, filling up to 50% of the tumour bulk; five lesions also showed a haemangiopericytoma-like pattern (figs 2 and 3). Higher magnifications revealed a spindle cell tumour with a storiform pattern, the shape of cells ranging from oval to slender and elongated ("myofibroblastic-like"). Besides the haemorrhagic areas, prominent erythrocyte extravasation was found diffusely between the tumour cells (fig 2). The sieve-like mixture of spindle cells and erythrocytes in five cases closely resembled the nodular stage of Kaposi's sarcoma. Some of the lesions also showed focal prominence of serum (cases 4, 6 and 22), fibrin and thrombotic material (case 6). In 18 lesions prominent iron deposition, often with multinucleate cells (11/33), was present. While no endothelial lining was seen in areas of massive haemorrhage, the five cases with the haemangiopericytoma-like pattern showed endothelial and pericytic cell layers beside diffuse erythrocyte extravasation. Moreover, all lesions were richly vascularised with numerous, mostly compressed capillaries. Occasional mitoses (<1/10 high power fields) were observed.

IMMUNOHISTOCHEMISTRY (TABLE 3)

Eighteen of 30 lesions available for immunohistochemistry stained positively for factor XIIIa, moderately in 11 cases (<25% of cells), mainly at the periphery, and more prominently in seven cases (>25% of cells) with diffuse reactivity. Similarly, 18 lesions showed immunolabelling with E9, an anti-metallothionein marker, the intensity ranging from focal (three cases with <5%) to diffuse (four cases with >50%). Metallothionein positive lesions either revealed more or less prominent iron deposition (11 cases) or were also positive for factor XIIIa (seven cases). Six AFHs exhibited noticeable (>90%), and 13 less prominent and/or focal immunoreactivity (25–75%) with NK1C3; mast cells (serving as an internal control) and giant cells were strongly positive. Similarly, variable labelling (25 to >90%) of fibrohistiocytic cells was seen with smooth muscle markers in 14 cases, including one case with haemangiopericytoma-like features. This reactivity (fig 4A) was associated with the "myofibroblastic-like" appearance of the infiltrate as well as prominent sclerosis. Pericyte and all endothelial cell markers also highlighted the prominent, partially haemangiopericytoma-like vascularity of all the lesions (fig 4B). Apart from a focal blush effect, vascular markers were otherwise negative.

Statistically, the combination of iron deposition and immunoreactivity for factor XIIIa gave significant results ($\chi^2 = 7.8$; DF=2; $p = 0.02$); all cases of AFH showed either prominent iron deposition ("late" lesions) or labelling for factor XIIIa ("early" lesions). Similarly,

Table 3 Histological and immunophenotypic data for the 33 cases of AFH

Case no.	Sclerosis	Iron deposition	Percentage labelling for			
			Factor XIIIa	Metallothionein (E9)	NK1C3 (CD57)	SMA
1	Yes	Yes	Negative	>90	Negative	Negative
2	No	No	75	Negative	>90	Negative
3	Yes*	No	25–50	Negative	50–75	Negative
4	Yes	Yes	25	25	25	50
5	Yes*	Yes†	NA	NA	NA	NA
6	Yes*	Yes†	Negative	25	Negative	25
7	Yes	Yes†	<5	50	>90	Negative
8	Yes*	No	50	50	50	25
9	Yes*	Yes†	<5	75	>90	>90
10	Yes	No	25	50	75	Negative
11	Yes	Yes	25	50	50	50
12	Yes*	Yes	Negative	25–50	50–75	75
13	Yes	No	Negative	Negative	Negative	Negative
14	Yes	Yes†	Negative	25	Negative	Negative
15	Yes	No	25	25	>90	Negative
16	Yes	Yes†	Negative	<5	25–50	Negative
17	Yes*	No	25	75	75	>90
18	Yes*	No	Negative	Negative	Negative	Negative
19	Yes*	Yes†	25	25	>90	25
20	Yes	Yes	Negative	Negative	25	Negative
21	Yes	Yes†	<5	50–75	25	25–50
22	Yes*	No	50	Negative	25	25–50
23	Yes	No	50	<5	>90	Negative
24	Yes*	Yes†	Negative	Negative	50	25
25	Yes*	No	Negative	Negative	Negative	25
26	Yes*	Yes†	Negative	Negative	Negative	25–50
27	Yes*	Yes†	NA	NA	NA	NA
28	Yes*	No	NA	NA	NA	NA
29	Yes*	No	25–50	Negative	Negative	Negative
30	Yes*	Yes	Negative	Negative	Negative	50
31	Yes	No	25	<5	75	Negative
32	Yes*	No	50	25	Negative	Negative
33	No	Yes	25	Negative	Negative	Negative

* Prominent sclerosis; † giant cells present; NA = not available.

the statistical combination of prominent sclerosis and staining for SMA was significant ($\chi^2 = 11.1$; DF = 1; $p = 0.001$) confirming that SMA positive “myofibroblastic” lesions also show prominent sclerosis. A moderate correlation ($\chi^2 = 4.3$; DF = 1; $p = 0.03$) was also seen between labelling for factor XIIIa and with NK1C3, indicating that these markers are often positive (or negative) within the same lesions. All other combinations (sclerosis and factor XIIIa, metallothionein or NK1C3 labelling, respectively; or iron deposition and metallothionein, SMA or NK1C3 labelling, respectively; or sclerosis and iron deposition; or, finally, immunophenotypic features with each other) were non-significant.

Discussion

Dermatofibroma is a common fibrohistiocytic tissue response. With the variable presence of tissue components, various designations such as (benign) fibrous histiocytoma, histiocytoma cutis, sclerosing haemangioma, nodular sub-epidermal fibrosis or fibrous xanthoma are or have been used synonymously. Moreover, over the past decade, numerous distinctive clinicopathological variants have been characterised by a single predominant feature in otherwise typical dermatofibromas. These may be cellular aspects, such as in dermatofibroma with monster cells,¹⁰ epithelioid¹¹ and multinucleate cell angiohistiocytoma,¹² atypical (“pseudo-sarcomatous”),^{13,14} and cellular benign fibrous histiocytoma,¹⁵ or the recently described variants of clear cell dermatofibroma¹⁶ as well as dermatofibroma with myofibroblastic differentiation⁶; or architectural peculiarities such as in deep penetrating¹⁷ and atrophic dermatofibroma,¹⁸ or palisading cutaneous,¹⁹ and

cholesterotic fibrous histiocytoma associated with hyperlipoproteinemia.²⁰ AFH falls into this second category and is characterised by prominent intralesional haemorrhage. This was seen in 2% (33/1496) of our dermatofibromas, which is identical with reports by Calonje and Fletcher.² Despite an otherwise typical clinical presentation for dermatofibromas, mainly on the lower legs of adult females, in two thirds of cases from our series the dermatofibromas were difficult to distinguish from melanocytic and/or vascular lesions, in particular nodular lesions of Kaposi’s sarcoma, as described previously.^{1,2}

In contrast to AFH the nodular stage of Kaposi’s sarcoma is a multifocal disorder with additional patch and plaque stages elsewhere. Histologically, the nodules often reveal, at their periphery, lymphangiomatoid and angiomatoid features characteristic of early patch and plaque lesions.²¹ Moreover, lesions are more irregularly arranged without epidermal hyperplasia, and often contain numerous plasma cells. In questionable cases the marked immunoreactivity for CD34 differentiates Kaposi’s sarcoma⁵ from AFH. Other markers are less helpful: ulex europaeus agglutinin, factor VIII or CD31 are often negative in the nodular stage of Kaposi’s sarcoma⁵; factor XIIIa may be positive in both AFH and Kaposi’s sarcoma²²; and labelling with NK1C3, E9, and for SMA in AFH is too inconsistent to be used reliably for differentiation from Kaposi’s sarcoma.

Differentiation from other vascular lesions is mainly of academic interest: spindle cell haemangioendothelioma²³ shows prominent cavernous vascular spaces with papillary projections and phleboliths; angiosarcoma²⁴ shows irregular dissection of collagen, at least focally

Figure 4 (A) Prominent immunoreactivity for SMA in AFH with notably slender and elongated ("myofibroblastic-like") cells (case 11). (B) AFH with haemangiopericytoma-like features nicely outlined by pericytes stained for SMA. Note the additional prominent vascularity of small compressed vessels between areas of storiform fibrohistiocytic response (case 31) (Harris's haematoxylin counterstain).

with some cellular atypia, multilayering and mitoses.

The other important differential diagnosis, angiomatoid malignant fibrous histiocytoma,²⁵ usually occurs in the deep subcutaneous tissue on the forearms of children and young adults. A central cystic, often blood-filled cavity is surrounded by a storiform tumour with monomorphic, rounded, eosinophilic, desmin positive cells, as well as giant cells, with a focal outer layer of lymphoplasmahistiocytic infiltrate with germinal centre formation. While one might consider these lesions as just deeply located counterparts of AFH, their biology seems slightly more aggressive, with more frequent recurrences (20%) and occasional metastases (1%).

Our histological and immunophenotypic findings indicate that these lesions develop predictably over time. AFH seems to reflect the beginning of a process, characterised by erythrocyte leakage, probably caused or at least favoured by trauma. This leads to noticeable intralesional iron deposition and, later, prominent giant cell formation as seen in haemosiderotic histiocytoma.²⁶ Immunohistochemically, early lesions lacking iron deposition are

factor XIIIa positive, older lesions with notable iron deposition in multinucleate siderophages are negative. Labelling for factor XIIIa indicates activity of a protease involved in tissue linkage mechanisms—for example, covalently connecting the numerous monomer structures of fibrin and collagen,²⁷ which is important in early lesions, but loses its importance in later stages. Similar results have been reported on deep penetrating³ and atrophic variants of dermatofibroma⁴ for factor XIIIa and anti-metallothionein labelling, which also inversely correlates with sclerosis, a feature of late lesions. In these series anti-metallothionein labelling was explained by metabolically active tissue reactions of early lesions which need many enzymes (for example, DNA polymerase) dependent on trace elements such as copper or zinc delivered by the apoprotein family of metallothioneins. However, no such correlation was seen in the present series. This may be because, on the one hand, AFHs show much less sclerosis than these other dermatofibroma variants,³⁴ thus blurring the distinction between early and late lesions. On the other hand, prominent haemorrhage causes liberation of iron which, as a trace element, interferes with metallothionein metabolism; thus, recurrent episodes of haemorrhage or notable iron deposition are expected to be paralleled by increased metallothionein expression, even in late lesions.

Other immunohistochemical results can also be correlated with histological findings. Areas of myofibroblastic differentiation, characterised by slender and elongated spindle cells and prominent sclerosis, generally react with smooth muscle markers. Immunoreactivity with NK1C3 (CD57) has recently been reported in a small series of dermatofibromas with prominent myofibroblastic differentiation.⁶ The present series confirmed these findings, and, additionally, revealed some moderate correlations with immunoreactivity for factor XIIIa. The significance of these findings is as yet unknown. Yet, in any case, all of these results fit the hypothesis that dermatofibromas are reactive, with varying clinicopathological and immunophenotypic profiles depending on the age of the lesions.

Our histopathological findings outline a rare haemangiopericytoma-like pattern in AFH. Clinicopathologically, these lesions are similar to all other AFHs. No haemangiopericytoma-like features were seen in a work up of nearly 1500 dermatofibromas. Only recently, Calonje *et al*¹⁵ mentioned haemangiopericytoma-like features in occasional cases of cellular benign fibrous histiocytoma. On the one hand, these findings indicate that haemangiopericytoma-like features are among the possible reaction mechanisms of the fibrohistiocytic tissue response. On the other hand, this documents that "haemangiopericytoma" is not a single entity, but a potpourri of various diseases resulting from a common connective tissue reaction pattern. Mentzel *et al*²⁸ looked at the similarities between infantile haemangiopericytoma and infantile myofibromatosis and concluded that the former represents an early

cellular variant of the latter. Similar conclusions can be drawn from a case report on infantile myofibromatosis in two siblings,²⁹ where excision of 21 lesions revealed that the lesions had the same time course. Adult haemangiopericytoma may have a similar reaction pattern to a variety of malignant tumours, such as monophasic synovial sarcoma, mesenchymal condrosarcoma, malignant glomus tumours and others.³⁰

In conclusion, AFHs, including a haemangiopericytoma-like variant, have a characteristic time dependent histological and immunophenotypic profile, clearly different from nodular type Kaposi's sarcoma.

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