

Angiomatoid variant of fibrous histiocytoma: a case report and review of literature

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Summary. Fibrous histiocytomas by themselves are not very common in the head and neck region. Apart from considering the above fact, this report describes a unique and relatively rare variant of the neoplasm – the angiomatoid fibrous histiocytoma (AFH) which has a characteristic appearance and predilection for young individuals that occurred in the left lower border of the mandible in a 13-year-old girl.

Angiomatoid fibrous histiocytoma is a distinct fibrohistiocytic tumour of children and young adults that combines features of both fibrohistiocytic and vascular neoplasm. It is considered to be a tumour of intermediate malignancy because of its less aggressive course in contrast to the conventional malignant fibrous histiocytoma. The authors would like to stress upon the fact that clinicians should not overlook swellings that may not appear distinct visually and therefore consider it to be a part of normal anatomy, dismiss it as an anomaly with no significance, or treat it injudiciously, for ultimately it may prove to be a tumour that would require appropriate treatment and follow-up.

Introduction

The angiomatoid fibrous histiocytoma (AFH) is a rare tumour of the soft tissue, which occurs mainly in children and young adults, and is of an intermediate malignancy grade. The group of tumours classified under intermediate (borderline) malignancy grade is characterized by local aggressiveness (manifested by a high tendency for local recurrence) but is accompanied by an extremely low rate of distant metastasis; the few metastases that develop do so only after repeated failures of control [1].

AFH was first described in 1979 by Enzinger [2] and was felt to be a variant of malignant fibrous histiocytoma. The lesion in lymph nodes of similar histology, however, was presented in the 23rd seminar of the American Society of Clinical Pathologists [3] as haemangioendothelioma. Similarly, Harriston and Reed [4] reported two lesions of similar appearance as aneurysmal sclerosing haemangioma of the skin. Thompson and Shear in 1984 [5], in their review of the literature on oral fibrous histiocytomas in the head and neck region, have only mentioned the angio-

matoid variant as the one that rarely affects the oral and maxillofacial region.

Enzinger [2] had reported that the tumour was more common in the extremities rather in the head and neck region (10%) or in the trunk. Santa Cruz and Kyriakos [6] have reported 17 cases of cutaneous AFH that was located most commonly in the extremities. Regezi *et al.* [7] had categorized three cases of angiomatoid in malignant fibrous histiocytoma but had not specified their location. Costa *et al.* [8], Sarkar *et al.* [9], Grossman *et al.* [10], Fan and Allen [11], McKenna *et al.* [12], Jacobs and Chevinsky [13], Denictolis [14], and Pai *et al.* [15] have reported cases, reviewed literature, and concluded that the extremities and trunk region were the predominant sites of occurrence (Table 1).

The average patient's age of AFH presentation ranged from 6 months to 43 years with a mean age of 13 years [2]. Jacobs and Chevinsky [13] in their review of literature and Santa Cruz and Kyriakos [6], Grossman *et al.* [10], Regezi *et al.* [7] had reported that this subtype most often presents itself in individuals younger than 20 years. Enzinger and Regezi [2,7] had shown only a slight male predominance.

In general, the lesions manifested as a swelling or as a nodular, multinodular, or cystic mass that

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Table 1. Reported cases of AFH.

Serial no	Reference no.	No. of cases in head and neck region	Total no. of AFH in the body
1.	[2]	4	41
2.	[32]	—	1
3.	[33]	—	1
4.	[7]	Not mentioned	3
5.	[27]	Not mentioned	6
6.	[28]	7	108
7.	[8]	—	1
8.	[34]	1 (neck)	20
9.	[20]	Not mentioned	19
10.	[19]	—	6
11.	[31]	—	1
12.	[14]	—	1
13.	[9]	—	1
14.	[15]	—	3
15.	[30]	—	1
16.	[10]	—	1
17.	[17]	Not mentioned	158 (all)
18.	[35]	—	1
19.	[22]	—	4
20.	[13]	—	1

was slow growing and that was located in the subcutis or lower dermis [10]. McKenna *et al.* [12] had described pigmentation of the nodule. In few cases, the lesions were well circumscribed and freely movable resembling lymph nodes. Pain and tenderness were rarely encountered [12]. Enzinger [2] reported preceding trauma to the site of the tumour in 10 of the 41 cases. Kim *et al.* [16] also described AFH arising after a documented history of minor trauma.

Fanburg, in a review study of 158 cases, revealed a gender ratio of 1:3 females:males, an age range of 2–71 years, a median size of 2.0 cm, and a distribution of extremities > trunk > head and neck, with 66% lesions occurring in areas of normal lymphoid tissue [17].

Enzinger [2] had described that the smallest of the nodules measured 0.7 cm in diameter; the largest 10 cm, and the medium dimension of primary tumour nodules measured 2.5 cm. Three features, occurring in varying proportion, characterize this lesion [2,11]. They are: **1** irregular solid masses and nodules of fibroblast- and histiocyte-like cells; **2** focal areas of haemorrhage-like spaces; and **3** chronic inflammatory cells, chiefly lymphocytes and plasma cells.

The proliferated fibroblast- and histiocyte-like cells have a round or elongated vesicular nuclei and an indistinct, pale eosinophilic cytoplasm [2,11]. Haemosiderin could be demonstrated in many cells and may account for the colour of some of the

tumours [2,15]. Intracellular lipid and multinucleated giant cells are less prominent. Multifocal haemorrhage is a striking feature that is predominant in many of the cases [2]. The continued extravasation of blood is believed to cause slit-like tissue cracks within those cellular areas of the lesion. These tissue spaces fill with blood and continue to enlarge under pressure to finally form the angiomatoid areas. The degree of nuclear atypia in the cells of AFH is modest. The mitotic figures may vary from 0 to 3 per high power field. Myxoid stromal changes may be rarely seen [2].

Various studies present conflicting results in relation to the tumour origin, which may correlate to the prognosis in that there may be a spectrum with angioma in one end and a fibrous histiocytoma in the other end.

The finding of Weibal–Palade bodies through electron microscopy in the endothelial cells of capillaries within the tumour could not prove its endothelial origin as every malignant tumour is nourished by numerous capillaries with endothelial cells showing the same bodies [8]. Immunoreactivity for alpha-1 anti-chymotrypsin (ACT) and vimentin was apparent in all lesions, and is useful for immunodiagnosis of histiocytic lesions although it has been found in a wide range of cell types. Nonreactivity of tumour cells to antibody leucocyte common antigen (LCA) rules in favour of a fibroblast origin rather than a haematopoietic origin for malignant fibrous histiocytoma (MFH) [18].

Whether the cell of origin is a fibroblast (which can differentiate towards a macrophage), or a more primitive cell of origin (which can differentiate toward both fibroblast and a macrophage), cannot be answered. The appearance of HLA-DR is significant. This may be a result of the participation of the tumour in the immune response [17], and could correlate to the phagocytic origin of tumour cells. Immunohistochemical staining performed in four cases showed all to be positive for lysozyme, and three to be positive for Mac387 and CD68 [11], which support their histiocytic origin.

The finding of keratin [7] reactivity has no correlation but the finding of desmin [19] may be an evidence of myoid differentiation, and the author [19] tentatively proposed redesignation of angiomatoid MFH as a low-grade myogenic sarcoma of uncertain histogenesis. Finberg proved that most of the desmin-positive cases with adjacent lymphoid infiltrate (67%) showed similar scattered, desmin-positive

cells in the surrounding lymphoid infiltrate, adjacent to the tumour. Muscle-specific and smooth muscle actins were seen in 14% of the cases. Heavy caldesmon was strongly positive in 3%, and calponin was focally positive in 73% and extensively positive in 12% of the cases. MYOD1, myoglobin, and myogenin (MYF4) were negative in all tumours studied. Forty-five percent of the cases were positive for CD99, and 52% of these had round cell morphology. Fifteen percent of these cases were positive for KP-1 (CD68). All tumours were positive for vimentin and were negative for CD21, CD35, S100 protein, CD34, keratins 8/18, and lysozyme [17].

The myoid, primarily myofibroblastic, phenotype of these lesions, is supported by desmin, calponin, and occasional actin positivity. The occasional heavy caldesmon and smooth muscle actin, additionally, suggest rare smooth muscle phenotype; however, the lack of skeletal muscle markers indicates no relationship of AFH to the skeletal muscle tumours. The resemblance of these lesions to lymph nodes, clinically and morphologically, the finding of similar desmin-positive cells in the adjacent lymphoid infiltrate, and the fact that 66% cases were found in sites of normal lymphoid tissue raise the possibility that some of these lesions may arise from or be related to, myoid cells of lymphoid tissue [17]. Desmin positivity was noted in 51% of the cases and occurred in both predominantly round cell and spindle cell tumours.

Similar studies for KP1 (CD68) indicate that the tumoral mesenchymal cells have acquired phagocytic capacities [11]. This explanation is supported by the relative restriction of CD68 to cells of monocyte/macrophage origin when Smith *et al.* [20,21] failed to identify this antigen within other mesenchymal tumours of various cell lines.

Electron microscopy showed a mixture of fibrohistiocytic, myofibroblastic, and undifferentiated cells containing cytoplasmic processes and dense-core granules [22]. It is important for accurate diagnosis of this peculiar soft-tissue tumour to recognize that it has a variety of immunophenotypes, such as histiocytic, myofibroblastic, epithelial, and neural, and may occasionally have predominantly round cell morphology.

Recently, genetic characterization of AFH has identified that the fusion of FUS and ATF-1 genes induced by a chromosomal translocation involving bands 12q13 and 16p11 could be complicated in tumour development [23].

When first described in 1979, AFH was felt to be a variant of malignant fibrous histiocytoma [2,7]. Because of its rarity, however, AFH has been difficult to classify and has been designated as a separate entity, rather than a subtype of MFH [9]. But the World Health Organization (WHO) [21,24,25] has categorized this tumour as a type of fibrous histiocytoma with an intermediate malignancy grade. Parham *et al.* [26] have classified AFH under grade I tumours which include certain paediatric tumours with little propensity for malignancy and show negative margins histologically after complete tumour excision. Using flow cytometry, El-Naggar *et al.* [27] examined six AFH that were diploid, and more importantly, which had a distinctly different ploidy pattern from other MFH variants. These differences strongly suggested that AFH is at the benign end of the clinicobiologic spectrum manifested by malignant fibrous histiocytoma.

Costa and Weiss [28] evaluated 108 examples of AFH with attention to their behaviour. Local recurrence was observed in 12% of cases, 4.7% developed metastasis and only one patient died of the disease after 17 years. Enzinger [2] showed that only 3 among 24 cases died after 24 years. Location in the head and neck region, however, was also associated with a greater possibility of recurrence and hence they felt it reasonable to classify this tumour as a fibrohistiocytic tumour of intermediate malignancy. AFH has an almost invariably benign behaviour, but the 1% metastatic rate warrants its classification as low-grade 'malignant' [17]. It would appear therefore that a biologically borderline status is appropriate for the neoplasm [29]. Fan and Allen [11] concur with the opinion that intrinsically, this is a low-grade tumour.

Complete surgical excision [10,14] has been recommended by most authors although Costa *et al.* [30] have treated AFH by radiotherapy after three post-surgical recurrences. Although local recurrences have been reported, AFH is considered to have a good prognosis, as the mortality figures are low.

Case report

A 13-year-old girl attended our outpatient department with the complaint of a slowly growing mass in the left lower jaw for the past 6 months. The patient did not have any previous history of trauma and her medical history was noncontributory. On examination, the lesion manifested as a nodular swelling only on



Fig. 1. Photograph shows swelling in relation to the left lower border of the mandible.

palpation, as it was located in the subcutis, deep in the epidermis and dermis of the left lower border and the angle of the mandible (Fig. 1). The swelling was approximately 4×2 cm in size, firm and nontender on palpation. The skin over the swelling was normal. The submandibular and submental nodes were not palpable. Intraoral examination did not reveal any findings. Her jaw movements were normal. She did not have any salivary dysfunction. Orthopantomogram did not show any abnormality. Haematological reports were within normal limits. Fine-needle aspiration revealed predominantly histiocyte-like cells with areas of haemorrhage. Subsequently, an incisional biopsy was performed under local anaesthesia and submitted for histopathological examination.

Pathological findings

Macroscopic findings

The excised specimen exhibited a brown colour and was firm to palpation. The specimen on cross-section appeared fusiform and predominantly contained irregular cystic spaces filled with clotted blood.

Histopathological findings

Microscopically, the biopsy specimen showed predominantly haemorrhagic and cystic spaces (Fig. 2) along with sheets of histiocyte-like cells (Fig. 3) containing haemosiderin and with few mitotic figures. In addition, a dense infiltrate of chronic inflammatory cells, especially lymphocytes and plasma cells, were evident both in the centre as well as in

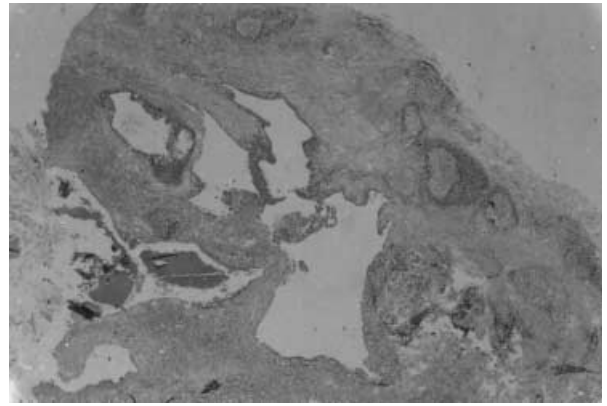


Fig. 2. Photomicrograph shows the cystic tumour surrounded by fibrocapsule along with blood-filled pseudovascular spaces (haematoxylin and eosin $\times 5$).

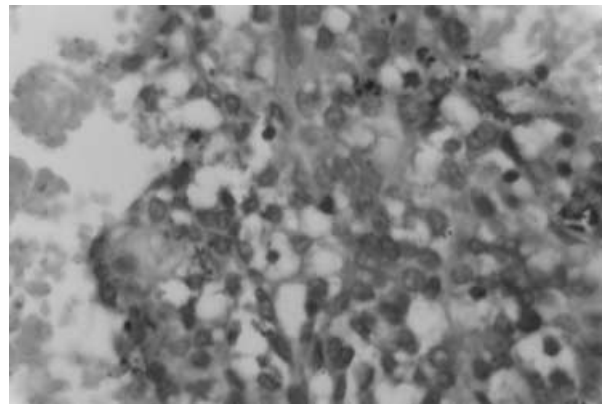


Fig. 3. Photomicrograph shows sheets of round as well as oval nuclei within faintly eosinophilic cytoplasm and few cells containing haemosiderin (haematoxylin and eosin $\times 40$).

the periphery where they often blended with areas of dense, partly hyalinized connective tissue forming a pseudocapsule. The haemorrhagic cystic spaces were lined by flattened tumour cells. Tumour cell infiltration was present in the underlying muscle tissue. These features were consistent with that of the angiomatoid variant of fibrous histiocytoma.

CD68 antigen immunoreactivity with MAb KPI (DAKO) was detected. A strong expression was evident among the tumour cells (Fig. 4) and was apparently confined to the cytoplasm. Reactivity for desmin and keratin (DAKO-USA), however, were negative.

The patient did not report for treatment for the next 3 months. Subsequently, the patient underwent an excision of the tumour with wide clearance under general anaesthesia and the postoperative

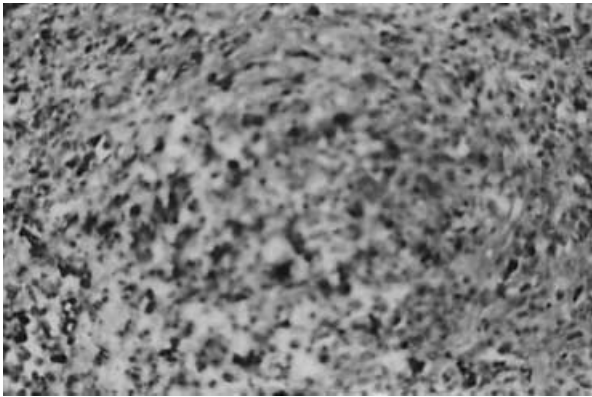


Fig. 4. Immunostaining shows CD68 expression ($\times 40$).

histopathological report was also consistent with the incisional biopsy report of angiomatoid fibrous histiocytoma. The patient is on a regular follow up.

Discussion

This article reports a case of angiomatoid variant of fibrous histiocytoma (AFH), a rare fibrous tissue tumour with unique clinical characteristics and prognosis. As described in the literature, the lesion presented itself at an early adult life of 13 years, in our case, however, at a rare site in the subcutis of the lower border and angle of the mandible as head and neck is not a common site of occurrence [17]. Moreover, the lesion, unlike in Enzinger [2] and Regezi's [7] series, which had shown slight male predominance, occurred in a female child.

The lesion presented itself as a nodular swelling that was slow growing and deep seated because of its location in the subcutis, and hence could not be appreciated visually as a distinct swelling. The clinical appearance may not even alarm the clinician and may be dismissed as a part of normal anatomy or a lymph node that may be enlarged because of a secondary infection, as 66% of lesions occur in areas of normal lymph node [17]. It is very important to keep in mind the possibility of the occurrence of rare lesions like AFH in children as otherwise they would be treated symptomatically, in contrast to the fact that AFH requires wide excision of the tumour along with normal margins as treatment since it is considered to be a fibrohistiocytic tumour of intermediate malignancy. Literature in Enzinger's [2] series of 24 cases, on follow-up information, reported that 15 patients developed local recurrence and 3 patients succumbed to the disease. In contrast,

Costa and Weiss [28] in their study showed that the recurrence and distant metastasis rate in AFH is extremely small. The explanation for this discrepancy between the two sets of data is best explained in that by early accurate diagnosis and prompt treatment, the prognosis for this lesion is good.

Histologically, the three features as described by Enzinger [2] were seen in the lesion of our case, namely: irregular solid masses, nodules of histiocyte-like cells, and fibroblasts with focal areas of haemorrhage-like spaces along with chronic inflammatory cells.

An important diagnostic error in reference to AFH is to mistake it for an organizing haematoma. The presence of extravasated erythrocytes with a spindle cell stroma may lead to erroneous diagnosis of vascular neoplasms like Kaposi's sarcoma, haemangioendothelioma, haemangiopericytoma, and angiosarcoma [8]. We clearly delineated all these lesions, however, as it should be remembered that broad, compact sheets of histiocyte-like cells are never observed in an organizing haematoma, as most of the cyst-like spaces are lined by several layers of histiocyte like cells, often with considerable deposits of haemosiderin in their cytoplasm. Moreover, other vascular neoplasms were excluded by the fact that dilated or branching vascular spaces are rare and never prominent or evenly distributed in AFH, as in haemangiopericytoma or haemangioendothelioma. Microhaemorrhages and extravasated erythrocytes occasionally raise the question of Kaposi disease, but our case did not display the typical spindle cell or slit-like pattern of Kaposi. Moreover, the absence of pleomorphism and presence of histiocyte-like cells along with the clinical duration ruled out angiosarcoma.

Immunohistochemical staining showed a strong positivity for CD68 and this could be interpreted in two ways. The first is that the line of differentiation of this tumour is similar to that of a tissue macrophage. The explanation for this fact is that the imputing cytokine production by these tumour cells attracts lymphocytes to the tumour that will remit on tumour removal. The second and perhaps the most likely explanation is that CD68 expression represents a phenotype alteration in a mesenchymal cell perhaps paralleling acquisition of lysosomes and an enhanced capacity for phagocytosis [11]. The negativity for desmin did not favour the possibility of myoid differentiation in our case.

Our patient is free of recurrence for the past 3 years, after complete wide excision along with normal

margins. Systemic symptoms, anaemia, and death, which occurred in Enzinger's series [2] and certain original cases recognized retrospectively, were invariably diagnosed as various types of benign conditions and were often treated suboptimally.

Although death from this tumour occurred only in one patient after a period of 17 years following prompt diagnosis and appropriate treatment in the Costa and Weiss series [28], along with the follow-up information from our case, it seems reasonable to consider this tumour as a fibrohistiocytic tumour of intermediate malignancy rather than as a form of malignant fibrous histiocytoma, the majority of which are high-grade sarcomas in adults. Its inclusion under the umbrella of fibrohistiocytic neoplasms does not imply that the cells of AFH necessarily possess the same functional and antigenic attributes as those of the adult forms of MFH. The cells in the latter tumour are closely related to fibroblast, whereas those in AFH have been variously compared with histiocytes.

To summarize, our patient manifested both clinically and histopathologically characteristic features of angiomatoid variant of fibrous histiocytoma. Immunoreactivity for CD68 and negativity for desmin indicate the macrophage lineage and the patient is so far free from recurrence after complete wide excision of the tumour for the past 3 years. The authors would finally like to stress upon the fact that clinicians should not overlook swellings that may not appear distinct visually and therefore consider it to be a part of normal anatomy, anomaly with no significance, or treat them injudiciously. As accurate diagnosis is mandatory to formulate an appropriate treatment plan and subsequent follow up on such clinically deceptive cases, greater responsibility for early diagnosis rests on the paedodontists and oral pathologists.

What this paper adds

- This paper adds to literature, angiomatoid variant of fibrous histiocytoma, a rare tumour of intermediate malignancy grade.

Why this paper is important to paediatric dentists

- The tumour had presented in the subcutis of mandible which is an unusual site of occurrence.
- The clinicians should not overlook swellings that may not appear distinct visually and therefore consider it to be a part of normal anatomy, anomaly with no significance or treat them injudiciously.

Acknowledgements

Our thanks to Dr Ramesha Rao, former Professor, Department of Pathology, Sri Ramachandra Medical College and Research Institute, Chennai; Dr Malikarjuna Rao, Apollo Cancer Hospitals, Chennai; Dr Padmanabhan, Department of Oral and Maxillofacial Surgery, Tamilnadu Government Dental College and Hospital, Chennai; and Ms Hamsika C. Mouli, Chennai.

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