Pediatr Radiol (2015) 45:1796–1802
DOI 10.1007/s00247-015-3404-y

ORIGINAL ARTICLE

Imaging of childhood angiomatoid fibrous histiocytoma with pathological correlation

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Received: 6 February 2015 / Revised: 28 April 2015 / Accepted: 1 June 2015 / Published online: 11 July 2015

Abstract
Background Angiomatoid fibrous histiocytoma is a rare soft-tissue tumor that more often affects children and young adults. There is little information available regarding the imaging appearance of angiomatoid fibrous histiocytoma in children.
Objective To describe the ultrasonographic (US) and magnetic resonance (MR) imaging findings of angiomatoid fibrous histiocytoma in children.
Materials and methods A retrospective analysis was done of US and MR imaging findings in children with angiomatoid fibrous histiocytoma. Clinical findings and histopathology with molecular analysis results were also collected.
Results There were 7 children with angiomatoid fibrous histiocytoma with a median age of 6 years (age range: 16 months-14 years). Patients presented clinically with a soft-tissue mass in the extremities or in the trunk. Four children had anemia, and three of them had additional systemic symptoms. Two patients had US and three had MR imaging while the remaining two had both. Lesion size ranged from 1.3 cm to 7.2 cm. In four patients, angiomatoid fibrous histiocytoma presented as a nonspecific predominantly solid mass. The other three patients had a combination of the following imaging findings: intralesional blood-filled cystic spaces with fluid-fluid levels, enhancing fibrous pseudocapsule and hemosiderin deposition. These findings correlated well with histopathology.
Conclusion The imaging detection of intralesional blood-filled cystic spaces with fluid-fluid levels, enhancing fibrous pseudocapsule and hemosiderin deposition in a soft-tissue tumor in a child may suggest the diagnosis of angiomatoid fibrous histiocytoma. A history of systemic symptoms and anemia in the presence of a soft-tissue mass may also be a clue for the diagnosis of angiomatoid fibrous histiocytoma.

Keywords Angiomatoid fibrous histiocytoma · Children · Pathology · Soft tissue · Ultrasound

Introduction

Angiomatoid fibrous histiocytoma is a rare soft-tissue mesenchymal neoplasm of uncertain histogenesis/line of differentiation that most commonly affects children and young adults [1]. The tumor carries intermediate malignant potential with low rates of recurrence and metastases and the overall prognosis is good [1, 2]. Patients usually present with a painless, slow-growing, deep subcutaneous mass in the extremities; however, the mass may also arise in other regions of the body including head and neck, trunk, retroperitoneum and lung [3, 4]. Although the clinical and histological findings of angiomatoid fibrous histiocytoma have been well-described in large series of patients, especially in adults, there is little information in the literature regarding its imaging findings, particularly in children [5–15].

In this study, we reviewed the ultrasound (US) and magnetic resonance (MR) imaging findings of angiomatoid fibrous histiocytoma in children in our patient population and compared these with clinical and pathology findings and with previously described cases in the literature.

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Materials and methods

The study was approved by the Research Ethics Board of our institution and patient consent was waived. Patients were identified through a search in the electronic database of pathology and imaging reports for the period Jan. 1, 1999, to June 30, 2013. Data regarding demographics, clinical history, findings on physical examination, laboratory findings and histology findings, including molecular analysis, were collected.

US and MR imaging studies of these patients were reviewed by two pediatric radiologists together (A. Y. with less than 1 year of post-fellowship experience and O. M. N. with more than 14 years of post-fellowship experience) and a consensus was achieved in case of discrepancy. Based on the review of the cases reported in the literature [5–15] and a preliminary review of some of the cases included in this series, the following imaging characteristics of the masses were assessed:

1. On both US and MR imaging: location, size, shape, contours, pseudocapsule.
2. On US: echogenicity, echotexture, calcification, fluid-fluid level, perilesional echogenicity, posterior acoustic enhancement, internal septa and flow pattern on color Doppler interrogation.
3. On MR imaging: T1 signal (compared to muscle), T2 signal (compared to muscle), contrast enhancement pattern, hemorrhagic fluid-fluid level, pseudocapsule (hypointense rim), hemosiderin and perilesional signal intensity.

Results

There were seven children with a diagnosis of angiomatoid fibrous histiocytoma. Five were male and 2 were female with a median age of 6 years and 3 months (age range: 16 months-14 years). Patients presented clinically with a soft-tissue mass located in the upper extremities (upper arm, shoulder and forearm), lower extremities (thigh and foot) or trunk (chest wall). Three children presented additionally with systemic symptoms for 6 months to 1 year, including fever and weight loss, and four children had anemia.

Five children had MR imaging and four had US; two had only US, three had only MR imaging and two had both.

On imaging, most of the lesions were subcutaneous, ovoid to round in shape, with well-defined contours. The lesion size ranged from 1.3 cm to 7.2 cm in maximum dimension. A description of the US and MR imaging findings in our patients is included in Table 1 and illustrated in Figs. 1, 2, 3, 4 and 5.

In three children, MR imaging revealed intralesional blood-filled cystic spaces with fluid-fluid levels and enhancing fibrous pseudocapsule, associated with hemosiderin deposition. These findings were confirmed on histopathology. Only one of these three children had US, which also demonstrated the presence of intralesional fluid-debris levels within large cystic spaces similar to MR imaging. In two of the other three children who also had US, few tiny cystic spaces were identified within a

Table 1 Summary of the ultrasound and magnetic resonance imaging findings in seven patients with angiomatoid fibrous histiocytoma

General features (7 patients)	Deep subcutaneous location – 4	Deep subcutaneous and intramuscular location – 1	Intermuscular location – 1	Intermuscular and intramuscular location – 1
	Ovoid shape – 3	Round shape – 2	Multilobulated – 1	Bilobed – 1
	Maximum dimension <3 cm – 4	Maximum dimension >3 cm – 3		
	No recurrence – 3	Recurrence – 1	Not available – 3	
Ultrasound features (4 patients)	Hypoechoic to subcutaneous fat, isoechoic to muscle – 3	Mixed: hypoechoic and hyperechoic to muscle – 1		
	Predominantly solid with tiny cystic areas, overall heterogeneous – 2	Solid, heterogeneous – 1	Cystic, heterogeneous – 1	
	Perilesional increased echoes – 3	No perilesional increased echoes – 1		
	Posterior acoustic enhancement – 4			
	Fine internal septa – 3	No fine internal septa – 1		
	Peripheral and central vascularity – 1	Peripheral vascularity – 1	Central vascularity – 1	Peripheral and septal vascularity – 1
Magnetic resonance imaging features (5 patients)	T1- and T2-hyperintense compared to muscle – 4	T1- and T2-hypointense compared to muscle – 1		
	Hemorrhagic fluid-fluid level – 3	No hemorrhagic fluid-fluid level – 2		
	Peripheral and septal enhancement – 2	Diffuse enhancement – 2	Peripheral enhancement – 1	
	Pseudocapsule – 3	No pseudocapsule – 2		
	Hemosiderin – 5			

All numbers in the table indicate the number of patients

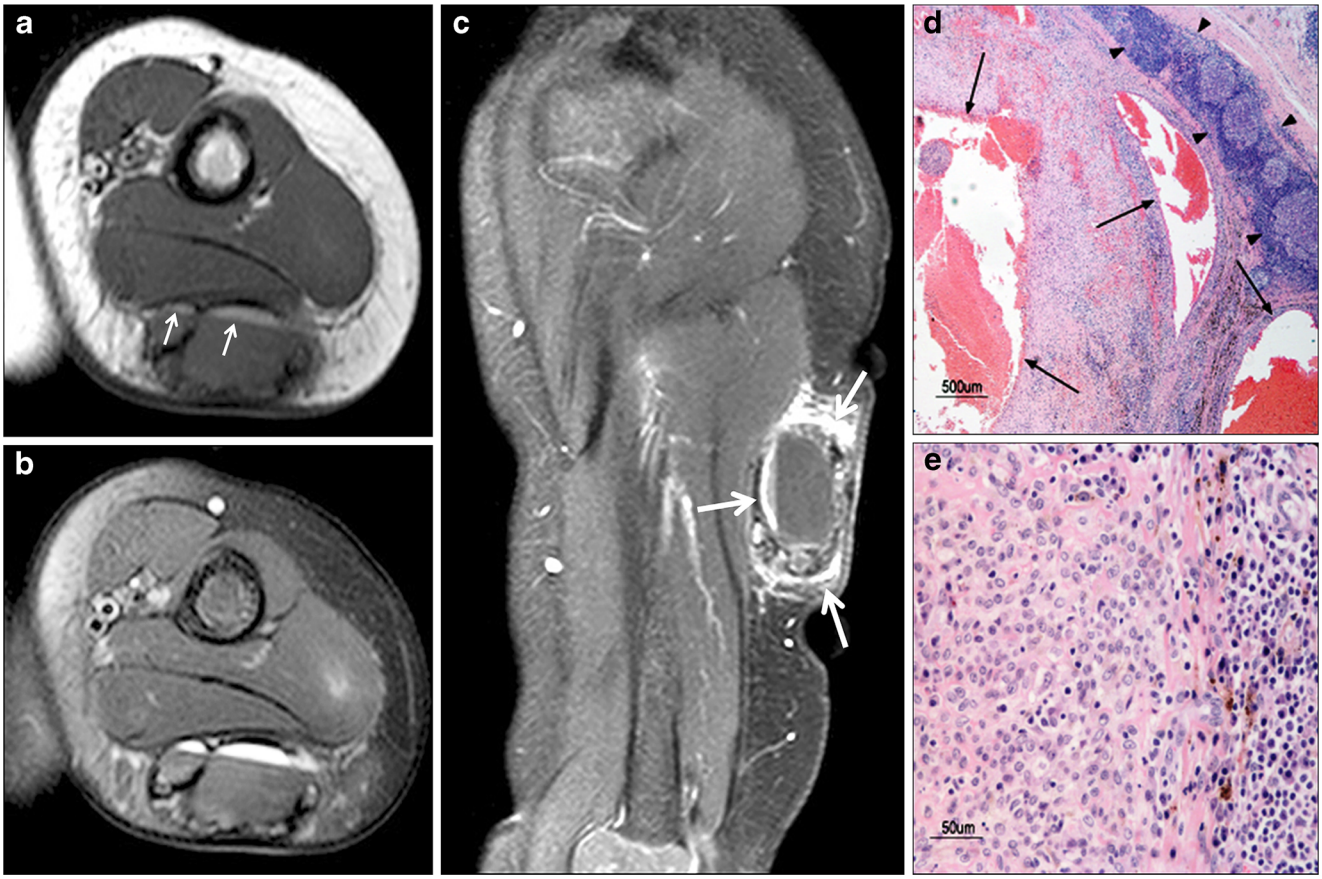

Fig. 1 A 16-month-old boy presented with a slowly enlarging soft-tissue mass in the posterior aspect of the mid-left upper arm. Axial T1-weighted (**a**), axial fat-suppressed T2-weighted (**b**) and sagittal gadolinium-enhanced fat-suppressed T1-weighted (**c**) MR images show a lobulated, multicystic mass confined to the subcutaneous tissues, with fluid-fluid levels in the two largest cysts. The nondependent fluid within the cysts is hyperintense on the T1-weighted image (*arrows*) (**a**) suggesting blood products. The cysts show a partial rim of low signal intensity on all sequences due to hemosiderin deposition. In (**c**), there is an outer enhancing rim due to the presence of a pseudocapsule (*arrows*). **d** Photomicrograph (H&E stain) shows cystic blood-filled spaces (*arrows*) within a well-circumscribed nodular mass that has a rim of reactive lymphoid tissue at its periphery (*arrowheads*). **e** Photomicrograph (H&E stain) shows myofibroblastic-like plump spindle cells forming the nodular mass. On the right-hand side, the reactive lymphocytic component is shown for comparison

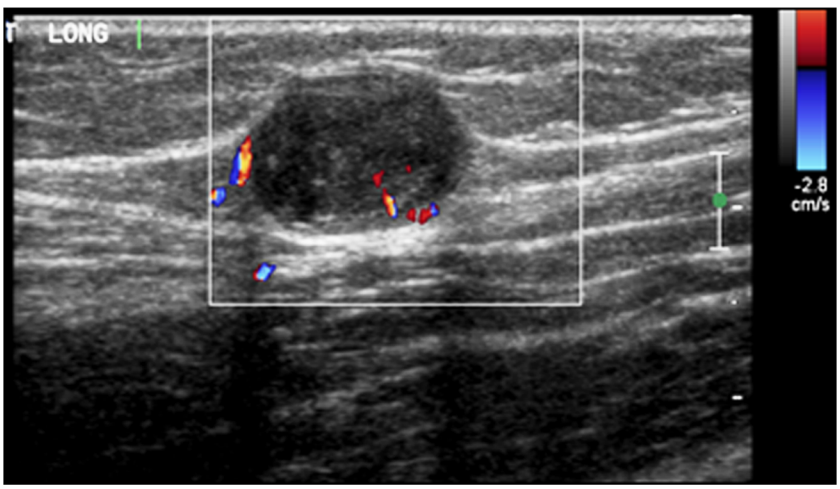

Fig. 2 A 3-year-old girl presented with a painless mass in the left thigh. Color Doppler US image shows a subcutaneous, heterogeneous, hypoechoic (compared to subcutaneous fat), ovoid lesion with well-defined contours abutting the superficial fascia. The lesion has a pseudocapsule, intralesional punctate hyperechoic foci suggestive of calcification, small cystic components and posterior acoustic enhancement. Peripheral and central flow is noted. The detection of vascularity is important to recognize the solid components of the lesion and to help differentiate from a complex cyst

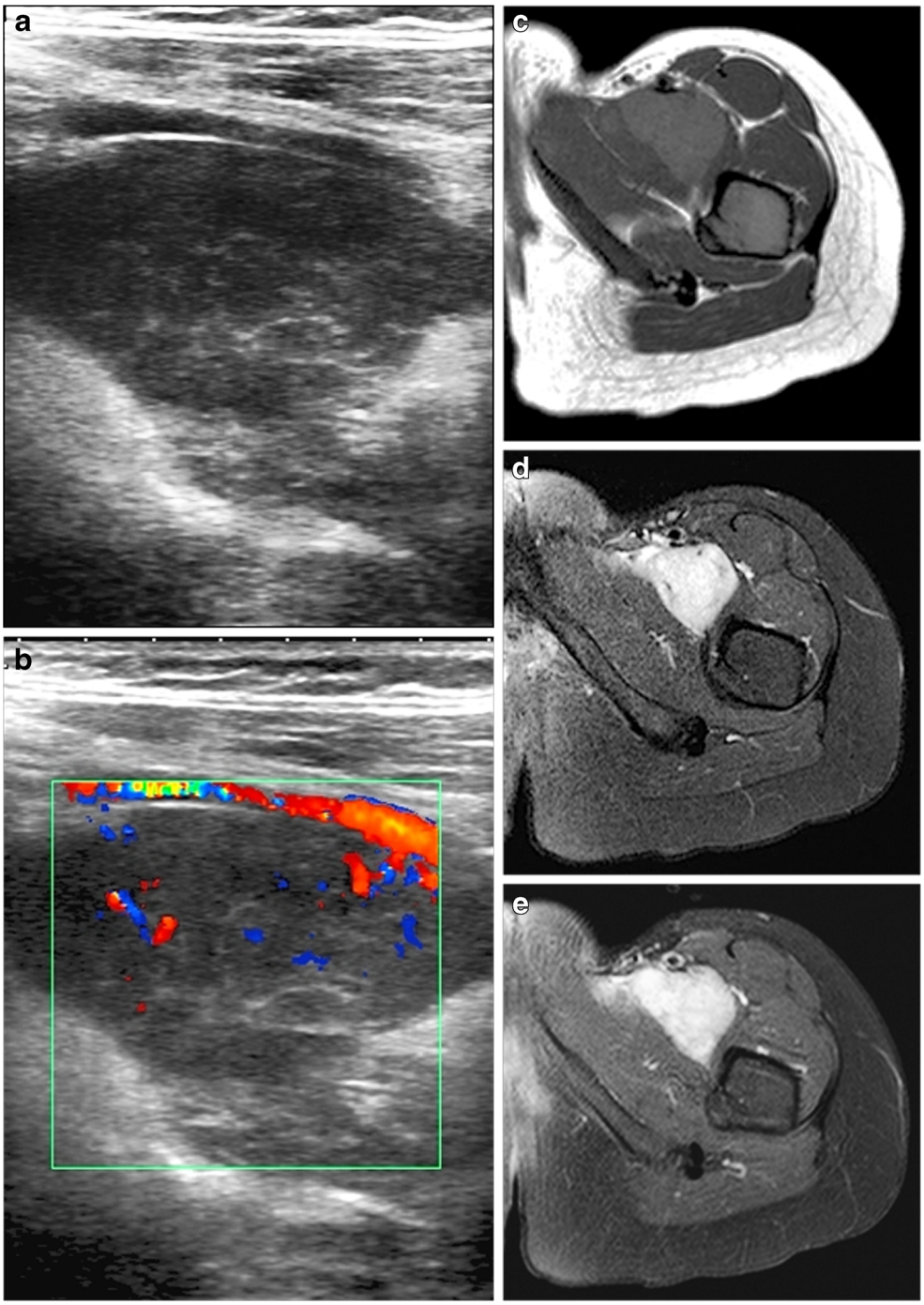

Fig. 3 A 10-year-old girl presented with a painless mass in the left thigh associated with fatigue, pallor and anemia. Gray-scale US (**a**), color Doppler US (**b**), and axial T1-weighted (**c**), fat-suppressed T2-weighted (**d**) and gadolinium-enhanced fat-suppressed T1-weighted (**e**) MR images show a heterogeneous, intermuscular lobulated solid lesion with well-defined margins. On US, the mass has overall hypoechoic echostructure with increased perilesional echogenicity (**a**). Color Doppler US shows internal flow (**b**). On MR imaging, the mass is hyperintense compared to muscle on T1-weighted (**c**) and T2-weighted (**d**) MR images and shows heterogeneous enhancement after gadolinium administration (**e**)

mass that otherwise had a solid appearance. These tiny cystic changes reflect the blood-filled cystic spaces noted on histopathology. In the remaining child, the lesion was solid without cystic spaces on both US and MRI and the absence of large cysts was confirmed on histopathology.

In addition to histopathological evaluation, some genetic aberrations associated with angiomatoid fibrous histiocytoma were also assessed on the tumor specimens in four children. In our study, molecular genetic analysis using reverse transcriptase–polymerase chain reaction (RT-PCR) on paraffin-extracted ribonucleic acid was found to be positive for t(12;22)(q13;q12) *EWS/ATF1*[1] fusion transcript in two children and was found to be positive for t(2;22)(q33;q12) (*CREB1*[2]*-EWSR1*[3]) in another child.

[1] Ewing sarcoma gene/activating transcription factor 1
[2] Cyclic AMP response element binding protein 1
[3] Ewing sarcoma breakpoint region 1

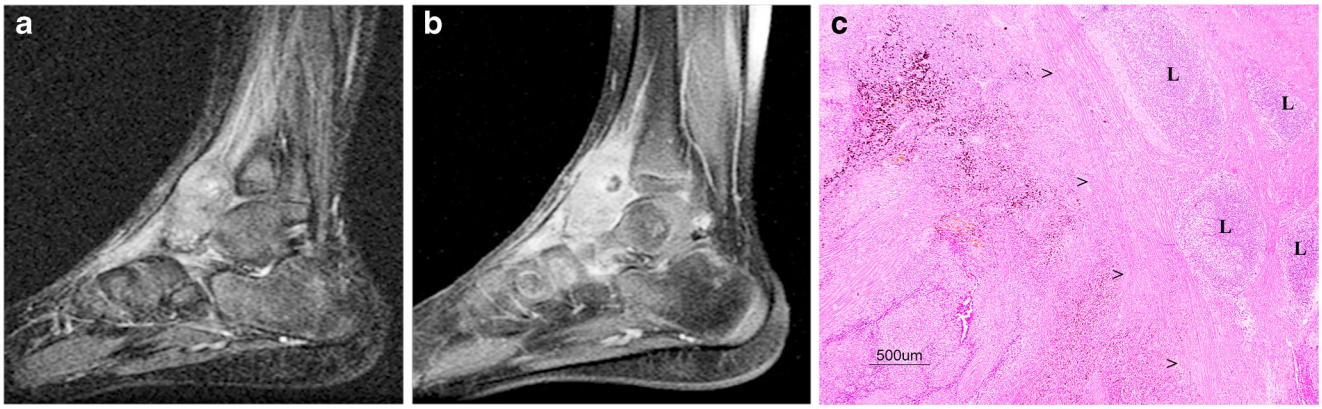

Fig. 4 A 6-year-old boy presented with a mass in the anterior aspect of the right ankle. There was also a history of weight loss. Sagittal fat-suppressed T2-weighted (**a**) and gadolinium-enhanced fat-suppressed T1-weighted (**b**) MR images show a mass involving the deep soft tissues in the right anterior ankle. The mass is extra-articular to the ankle joint and deep to the extensor tendons. It is slightly hyperintense to muscle and heterogeneous on the T2-weighted image (**a**) and shows mild diffuse enhancement post gadolinium administration except for a small cystic area posterosuperiorly (**b**). No fluid-fluid levels are noted. However, a peripheral linear low signal intensity inferiorly reflecting hemosiderin deposition is seen. **c** Photomicrograph (H&E stain) shows the fibrous wall of the mass (*arrowheads*). External to the wall are collections of reactive lymphoid follicles (*L*). The lesion is on the left side of the wall where collections of pigmented (iron from previous hemorrhages and lipofucsin) macrophages are present. The *lower left* corner shows mixed spindle-shape and epithelioid-appearing fibrohistiocytic cells that form the lesion

Discussion

Angiomatoid fibrous histiocytoma is an uncommon soft-tissue tumor that in the past was considered a subtype of malignant fibrous histiocytoma. However, in the revised World Health Organization classifications of soft-tissue tumors of 2002 and 2013, angiomatoid fibrous histiocytoma has been included in the category of "tumors of uncertain differentiation" as the cell line that gives origin to this tumor remains a topic of debate [1, 16, 17]. Apart from some distinct morphological features on histopathology, angiomatoid fibrous histiocytoma has clinical features that are different from the other subtypes of the tumor previously known as malignant fibrous histiocytoma, including earlier age of presentation, more superficial location, lower metastatic potential and overall good prognosis [1, 2, 17, 18].

Angiomatoid fibrous histiocytoma has been reported in patients as young as 2 months and as old as 71 years, but typically affects individuals 30 years or younger [9]. This is also reflected in our series with a wide age range of presentation in children between 16 months and 14 years of age.

The tumor tends to be relatively superficial usually affecting the deep dermis or subcutaneous tissues. Involvement of deeper soft tissues is less commonly described although in

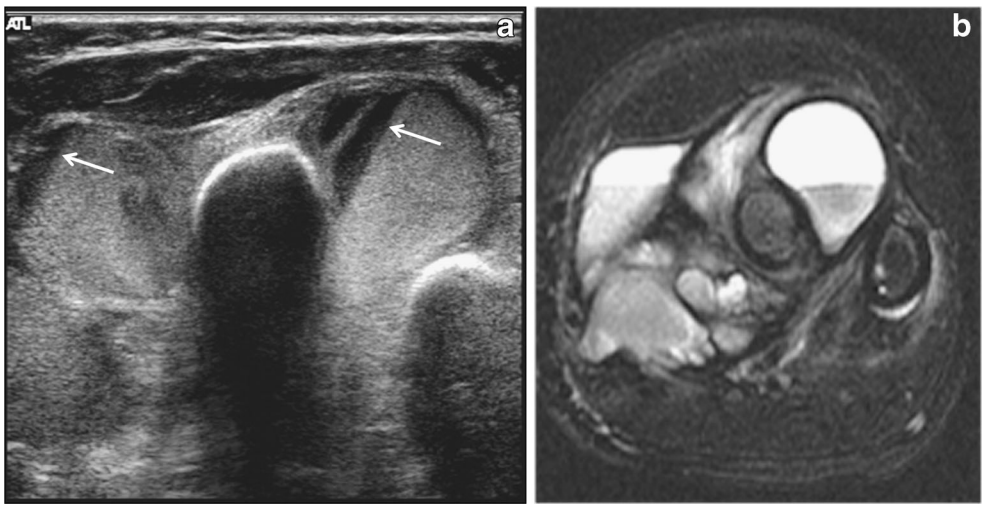

Fig. 5 A 12-year-old boy presented with a 6-month history of forearm swelling, weight loss, night sweats, intermittent fever and decreased appetite. Transverse US scan (**a**) shows a lobulated multicystic mass with fluid-debris levels (*arrows*). Axial fat-suppressed T2-weighted (**b**) MR image shows a large, lobulated, solid and cystic mass in the deep soft tissues involving the muscles of the flexor and extensor compartments. Fluid-fluid levels are present in the cystic spaces. Low signal intensity in the walls of the cysts in (**b**) is consistent with hemosiderin deposition

two of our patients the mass involved the muscle planes. Our series also confirmed that the extremities are most common site of involvement, although cases occurring in the trunk and even head and neck are well documented [2, 3, 13]. The tumor often presents as a slow-growing mass without any other symptoms. However, in some patients there may be associated systemic symptoms such as fever, malaise, weight loss and anemia as was seen in three of our patients [5, 9, 13]. This is an important clue that may help in the differential diagnosis. The explanation for the systemic symptoms is unknown but may be cytokine production by the tumor and their presence is not necessarily related to local recurrence or metastatic disease [12].

Angiomatoid fibrous histiocytoma is considered to be a tumor of intermediate malignancy with reported local recurrence rates of 11-16%; in some series, no recurrence has been reported when tumor-free margins are achieved during surgery [12, 18, 19]. Similarly, there is a low reported occurrence of metastases of 1–5% [12, 18, 19]. In our study, only one child had local recurrence. In the remainder of the children in our series, no local or distant metastases were diagnosed. Given the relatively benign clinical course, the current recommendations for management of angiomatoid fibrous histiocytoma indicate that local resection is usually sufficient [18].

The histopathological features of angiomatoid fibrous histiocytoma have been well-described in the literature. Typical findings include a dense fibrous pseudocapsule, a peritumoral lymphoplasmacytic infiltrate, blood-filled cystic (pseudoangiomatoid) spaces lined by tumor cells rather than true endothelium, with stromal hemorrhage or hemosiderin deposition, and multinodular aggregates of histiocytoid and spindle-shaped tumor cells in a whorled, sheet-like or fascicular growth pattern, and with a low mitotic rate [1, 2]. Molecular studies including RT-PCR analysis and fluorescence in situ hybridization (FISH) procedures using split signal probes to *EWSR1* and *FUS*[4] may detect the three related types of translocations associated with angiomatoid fibrous histiocytoma [15, 20, 21]. In our series, three of four tumors that underwent these molecular genetic analyses were found to be positive for these genetic aberrations.

US and MR imaging are the preferred imaging methods for evaluation of soft-tissue masses. The US and MR imaging findings of angiomatoid fibrous histiocytoma have only been reported as case reports in the literature, mainly in adults. Four previous pediatric cases have been illustrated in the literature [5, 8, 12, 14], all of them evaluated with MR imaging only and showing features also noted in our series. To the best of our knowledge, US findings have been described only in one case report in a 77-year-old woman with a lesion in the temporal region [13]. US showed an irregular-shaped, hypoechoic, cystic lesion with peripheral flow. US elastography revealed high elasticity centrally. In our series, four children had US. In three children, the mass had a predominantly solid appearance, of which there were tiny cystic changes in two, and in one the mass had a multicystic appearance with fluid-fluid levels of mixed echogenicity and septal/peripheral vascularity. These cystic changes of varying size are in keeping with the blood-filled cystic spaces noted on histopathology.

Some MR imaging features of angiomatoid fibrous histiocytoma previously described in the literature may help in the diagnosis although none is considered to be specific. The most notable and helpful MR imaging finding is the presence of cystic spaces with fluid-fluid levels [9], which were noted in three of our patients and in two of the four children previously illustrated in the literature [5, 14]. Similar as with US, these represent the blood-filled cystic spaces seen on histopathology. However, hemorrhagic fluid-fluid levels can also be part of other pediatric soft-tissue masses of both benign and malignant etiologies, including hematoma, lymphatic malformation, venous malformation and synovial sarcoma, and these should be considered in the differential diagnosis [9, 12, 22, 23]. The literature does not provide a good explanation for the cause of intralesional hemorrhage and in our series they do not seem to be related to another etiology such as trauma. Angiomatoid fibrous histiocytoma may also show hemosiderin deposition, which was noted in all five patients who had MR imaging. These appeared as dark areas with susceptibility and correlated well with findings on histopathology.

A fibrous pseudocapsule was observed as a peripheral well-defined, hypointense, rim-like area on T1- and T2-weighted images with avid enhancement after gadolinium administration. In four out of five cases with MR imaging, the lesions appeared hyperintense compared to muscle on T1- and T2-weighted images. However, there is a wide range of signal intensity reported in the literature. Perilesional edema was seen in three out of five patients with MR imaging, likely representing reactive edema since no tumor infiltration was noted within this area on histopathology.

The diagnosis of soft-tissue tumors is often challenging as most will often have nonspecific imaging features. However, we attempted to find some imaging characteristics that may help to establish the diagnosis of angiomatoid fibrous histiocytoma. The main limitation of our study is the relatively small number of the subjects due to the rarity of this entity. Nevertheless, we hope that our case series will serve as a baseline for future studies, particularly in children. A multi-institutional study will be necessary to collect a larger sample size.

Conclusion

The imaging findings of intralesional cystic spaces with fluid-fluid levels, hemosiderin deposition and enhancing fibrous

[4] Fused in sarcoma

pseudocapsule may suggest the diagnosis of angiomatoid fibrous histiocytoma. It is important to note that these findings, which are best demonstrated on MR imaging, are not specific and may not be present in all patients. Additionally, the presence of a soft-tissue mass combined with a history of systemic constitutional symptoms and anemia may also be a clue for the diagnosis of angiomatoid fibrous histiocytoma in children.

Conflicts of interest None

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