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CASE REPORT

Angiomatoid fibrous histiocytoma – an adolescent with an unusual presentation and course

Sara Isabel de Almeida[1], Sofia Cochito Sousa[2], Cristina Mendes[3], Rafael Cabrera[3], and Ana Lacerda[3]*

[1]Paediatric Department, Hospital Beatriz Ângelo, Loures; [2]Paediatric Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon; [3]Department of Paediatric Oncology, Portuguese Institute of Oncology, Lisbon. Portugal

Abstract

Introduction: Angiomatoid fibrous histiocytoma is a rare soft tissue neoplasm, which usually presents as an indolent mass in children and young adults and is often mistaken for a hematoma or hemangioma. Suspecting this diagnosis from imaging findings may be challenging, leading to diagnostic delays. Prognosis is generally favorable and metastases are infrequent at presentation. **Case report:** We describe the case of an adolescent who presented with a two-month history of a growing mass in the left scapular region, where diagnosis was made possible through surgical biopsy. **Discussion:** There were loco-regional lymphatic invasions and lung metastases at admission, and despite surgery and chemotherapy the disease rapidly progressed to death.

Keywords: Child. Histiocytoma malignant fibrous. Neoplasm metastasis. Soft tissue injuries. Soft tissue neoplasms.

Histiocitoma fibroso angiomatóide — um adolescente com apresentação e curso clínico atípicos

Resumo

Introdução: O histiocitoma fibroso angiomatóide é uma neoplasia rara de tecidos moles, que se apresenta geralmente como uma massa indolente em crianças e adultos jovens, sendo com frequência confundida com um hematoma ou hemangioma. Suspeitar desta entidade através da imagiologia pode ser desafiante, levando a atraso diagnóstico. O prognóstico é habitualmente favorável e as metástases são pouco frequentes na apresentação inicial. **Relato de caso:** Apresentamos o caso de um adolescente com uma massa com crescimento progressivo com 2 meses de evolução na região escapular esquerda, cujo diagnóstico foi possível através de biópsia cirúrgica. Na admissão apresentava envolvimentos dos gânglios linfáticos loco-regionais e metástases pulmonares. **Discussão:** Apesar de excisão cirúrgica e quimioterapia, ocorreu rápida progressão da doença com desfecho fatal.

Palavras-chave: Histiocitoma fibroso maligno. Neoplasia metastática. Lesões de tecidos moles. Neoplasias de tecidos moles.

***Correspondence:**
Sara Isabel de Almeida
E-mail: saraisabelalmeida@gmail.com

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Keypoints

What is known

- AFH is a rare soft tissue tumor usually presenting in children and young adults.
- Differential diagnosis of AFH includes hematoma and hemangioma, making it challenging.
- It generally has a benign course. Metastatic disease is infrequent, especially at presentation.

What is added

- Despite its generally benign course, atypical cases may present metastases at the initial examination and a high degree of suspicion is needed.
- Metastases are most commonly found in regional lymph nodes and the lungs, the latter generally associated with a fatal outcome.
- AFH's malignant potential is not yet fully understood, and treatment options should take this into account.

Introduction

Angiomatoid fibrous histiocytoma (AFH) is a rare soft tissue neoplasm which was first described by Enzinger in 1979 as an "angiomatoid malignant fibrous histiocytoma"[1]. Although uncertainty remains about the precise line of differentiation, it is currently no longer considered "malignant" due to its benign microscopic presentation and favorable prognosis. As such, since 2013 the World Health Organization has classified AFH as an "intermediate tumor of uncertain differentiation"[2,3].

AFH represents approximately 0.3% of all soft tissue tumours[4], affecting mostly children and young adults (median age at diagnosis of 14 and 20 years of age in two case series)[5,6]. It presents as a soft tissue mass in the deep dermis and subcutis of the extremities[7,8], usually indolent and with tenderness or pain, meaning it is often mistaken for a hematoma or a hemangioma[9]. Most patients have a good prognosis since the disease is metastatic in less than 1% of cases and the recurrence rate is lower than 15%[10,11]. But while it usually has a benign course, the malignant potential of this neoplasm is revealed by some descriptions of metastatic disease leading to death (in up to 14.3% of cases)[8].

In this report we present a case of AFH in a male teenager, emphasizing the diagnostic challenges and the rare aggressive progression of the disease.

Case report

A 13-year-old male born in Guinea-Bissau was referred at age 11 to a children's hospital in Europe for endocrine evaluation due to his tall stature, morbid obesity (maximum weight of 145 kg and body mass index of 39 kg/m^2), type 2 diabetes mellitus and hepatic steatosis. After being referred, he was under regular follow-up in a pediatric endocrinology unit, being treated with metformin.

He presented to the pediatric emergency department with a 24-hour history of bilateral temporal headache. While there, he incidentally complained of a mass in the left scapular region that he had noticed two months previously, which had gradually grown since then. The mass was painless and there were no local inflammatory signs. He also reported anorexia, with 18% weight loss (24 kg) during the previous six months, and fatigue. He denied any other symptoms, namely fever, asthenia, anorexia, night sweats, respiratory compromise or mobility impairment.

The laboratory tests revealed anemia (hemoglobin 6.5 g/dL), thrombocytosis (platelets 791000/μL), elevated LDH (1388 U/L, normal range [NR] 100-250 U/L), AST (61 U/L, NR 0-40 U/L), GGT (73 U/L, NR 0-60 U/L) and C-reactive protein (9.95 mg/dL, NR < 0.5 mg/dL). Total bilirubin and the erythrocyte sedimentation rate were normal. SARS-CoV-2 was identified in nasopharyngeal secretions.

A computerized tomography (CT) showed a large (15 x 12 x 8.5 cm) soft tissue mass involving the posterior muscle group of the left shoulder, presumably centered on the infraspinatus, with regular contours, not enhanced by contrast, but with a lower liquid level with high density, suggestive of a recent hemorrhage (Fig. 1), and a slight diffuse parietal thickening and at least one regular, slightly thickened septation. There were no underlying scapular bone changes. In the lung, there were multiple bilateral rounded images, suggestive of secondary lesions, coexisting with diffuse ground-glass opacities that were interpreted as being caused by SARS-CoV-2 pneumonia. There were also a few repletion defects in the subsegmental branches at the lung bases, suggesting peripheral pulmonary embolism, for which he was started on enoxaparin. He also started enalapril due to newly-diagnosed arterial hypertension. Due to the pandemic, he had to be admitted to a COVID-19 ward despite the oncological suspicion until the SARS-CoV-2 infection was resolved and later transferred to a pediatric oncology department when he was SARS-CoV-2 negative.

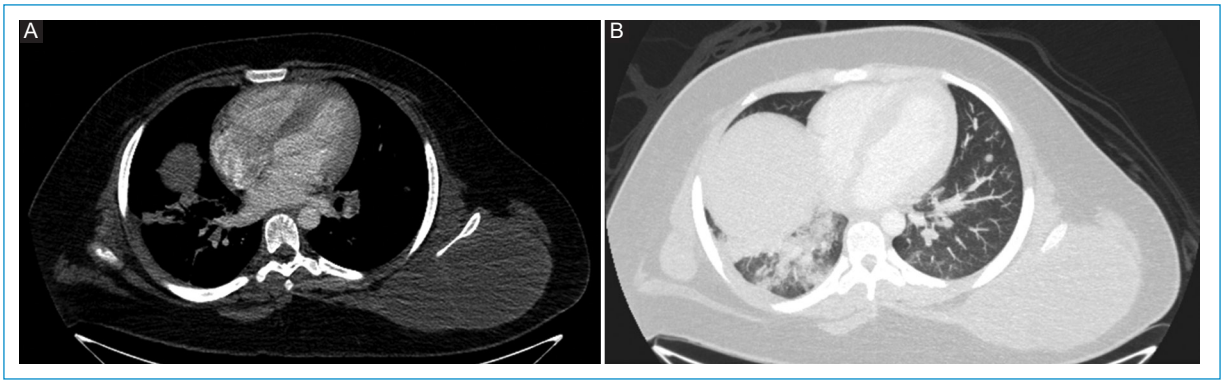

Figure 1. Axial mediastinal window **A:** CT image showing a mass involving the posterior muscle group of the left shoulder, apparently centered on the infraspinatus, with regular contours, with a lower liquid level with high density, suggestive of a recent hemorrhage; and lung window **B:** CT image where it is possible to identify a rounded lesion in the left inferior lobe, suggestive of metastasis, and ground-glass opacities in both inferior lobes.

To help establish a diagnosis and staging, an 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) with CT was performed. It showed a large soft tissue lesion (19 x 13 x 20 cm) of the scapular region, mainly with low uptake, but showing peripheral uptake (SUV max. 8.4) and uptake in the left axillary lymph nodes (SUV max. 4.3), with no significant uptake by the lung lesions.

The first two image-guided biopsies of the left scapular mass were inconclusive. Seven weeks after presentation, when he finally gathered clinical conditions, he was taken to the operating room, where a large septate hematoma (30 x 10 cm) was identified. The surgeon drained three liters of blood, performed a biopsy and surgical resection to the extent possible.

Histological examination revealed a large hematoma with a fibrous pseudocapsule, with reparative changes, fibrin deposition and inflammation. In some areas, nodules of a mesenchymal lesion with cystic pseudoangiomatous spaces were seen. They were composed of plump spindle and epithelioid cells with scant cytoplasm, with an occasional lymphoplasmacytic peripheral infiltrate (Fig. 2). Neoplastic cells were positive for CD99, desmin and synaptophysin, whereas myogenin and MyoD1 were negative. EWSR1 gene rearrangements (22q12.2) were confirmed by FISH and the array CGH also revealed the loss of chromosome 14 and partial loss of chromosomic regions 22q12-q13. Postoperative magnetic resonance imaging (MRI) revealed recurrent left scapular mass (14.8 x 5.7 cm) with a diffusely heterogeneous pseudocapsule of hematic content, supraclavicular and axillary lymph nodes (the largest measuring 4.1 cm, with hematic content) and the pulmonary lesions already revealed in the previous CT were also observed, presenting with contrast enhancement.

Clinical progression of the scapular mass was observed during the postoperative period. These findings were consistent with the diagnosis of AFH with associated hemorrhage, with regional (lymph node) and distant (bilateral lung) metastases.

He was started on chemotherapy with doxorubicin and ifosfamide, according to the non-rhabdomyosarcoma soft tissue sarcoma 2005 protocol (EpSSG non-rhabdomyosarcoma soft tissue sarcomas). However, local and metastatic progression was observed after three cycles of chemotherapy, including the development of alveolar hemorrhage. He also developed severe acute renal injury (creatinine 7.85 mg/dL and GFR 16 mL/min/1.73 m^2), probably secondary to the chemotherapy toxicity, and pulmonary aspergillosis, whose diagnosis was based on clinical presentation (fever, dyspnea and chest pain) and radiological findings on CT (multiple solid nodules surrounded by a halo of ground-glass opacity revealing the probable cause of alveolar hemorrhage due to angioinvasive aspergillosis). Bronchoalveolar lavage could not be performed due to the lack of safe clinical conditions.

In view of these complications and the manifest incurability, his family decided to return to Guinea-Bissau providing him with supportive measures only, including pain relief, medical treatment for acute renal injury and referral to the local hospital for follow-up. He died two months later, seven months after diagnosis.

Discussion

This case highlights the importance of the initial workup and suspicion since AFH is often mistaken for

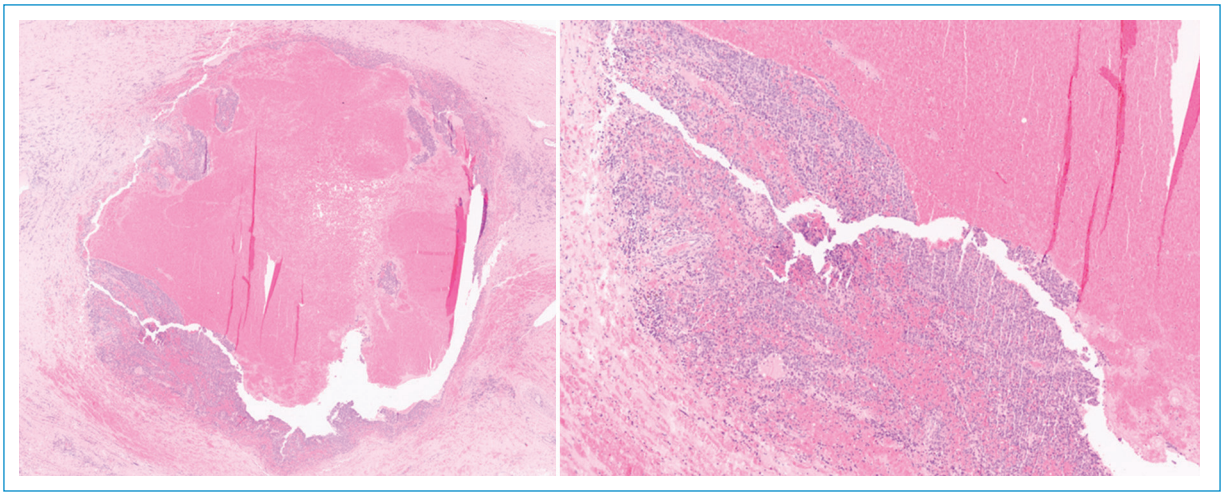

Figure 2. Low-power view of a tumor nodule with a pseudoangiomatous central cystic space, surrounded by fibrin and fibrous tissue (left). On medium power, a monotonous population of round cells with scant cytoplasm can be seen (right). Through immunohistochemistry, these cells tested positive for CD99 and desmin (not shown).

more common lesions, such as post-traumatic hematomas or vascular malformations or tumors, leading to a delayed diagnosis and treatment[8,12].

Most cases present as an indolent and painless mass, even though some reports refer to local tenderness and systemic symptoms[9]. In our case, medical care was sought due to acute symptoms, probably related to a SARS-CoV-2 infection, and the patient incidentally complained of a painless mass, weight loss and fatigue.

Ultrasonography and MRI are the preferred methods to evaluate soft tissue masses[13]. However, the imaging findings of AFH are nonspecific[12,14] and the absence of pathognomonic signs and characteristics, as well as the rarity of this tumor, may lead to diagnostic delays and/or misdiagnoses. Some reports reveal some common, yet nonspecific features which include intralesional cystic areas with fluid-fluid levels, an enhanced fibrous pseudocapsule, hemosiderin, and in some cases perilesional oedema[12-14]. FDG PET-CT can be used for staging and treatment response, however the interpretation of this must be well-considered, since the biopsy of suspicious nodes was frequently found to be benign in the histopathological examination[15,16].

Uncommonly, and in contrast with the often benign course of AFH, in our case, the first evaluation revealed loco-regional nodal and bilateral lung metastases. While Enzinger et al. described a series of 24 cases with 21% showing metastatic disease and with 12% deaths[1], Fanburg et al., describing 158 patients, reported only 1% metastatic cases, 2% with recurrences and no deaths[6]. However, these case series were published before recent advances in cytogenetic testing and therefore may have included other malignant neoplasms. More recently, Saito et al. reported a series of seven cases in which two patients presented with tumor recurrence and metastases and one of whom died from disease progression[8]. When present, metastases are most commonly found in regional lymph nodes and lungs, but may also present in the brain, liver and bone[17,18]. Certain factors are associated with an increased probability of local and distant metastases, namely head and neck locations, the tumor depth and irregular margins[5].

Our case is one of a few reports of AFH with nodal and lung metastases at the time of diagnosis and with a fatal outcome. Potter et al. described a three-year-old boy who also presented with nodal and lung metastases at diagnosis but had a good response to tocilizumab[19], which was not considered in our patient due to the lack of clinical conditions. A literature review identified 16 cases of metastatic AFH described in the last four decades, none of which had metastasis at diagnosis, which appeared between five months and 16 years after resection of the primary tumour[18]. However, the occurrence of lung metastases was universally linked to a fatal outcome.

In our case, the morbid obesity of the adolescent and the contingencies related to the COVID-19 pandemic may have contributed to a delayed presentation, diagnosis, and most of all to the fatal outcome.

The diagnosis of AFH is based on histopathology and immunohistology findings[8,9,13,14]. If the pathognomonic hallmarks of the disease are present in the histological examination, it is often possible to make a relatively straightforward diagnosis. These include a dense fibrous pseudocapsule, a perilesional lymphoplasmacytic

infiltrate, blood-filled cystic areas lined with tumor cells, with stromal hemorrhage or hemosiderin deposition, and multinodular aggregates of histiocytoid and spindle-shaped tumor cells in a fascicular growth pattern[1,2,20,21]. Further immunohistochemical studies may help distinguish AFH from other lesions, with the cells often showing positivity for CD68, CD99, epithelial membrane antigen and desmin at variable frequencies[19,20], a pattern displayed in our case.

As for molecular analysis, RT-PCR and FISH studies may detect the three translocations that have been associated with AFH: *FUS-ATF1, EWSR1-ATF1, or EWSR1-CREB1* fusion genes[13,21,22]. Rearrangements of *EWSR1* are common in AFH (present in 76% in a case series) and are therefore useful in confirming this diagnosis[21,23], as happened in our case. No specific rearrangement is associated with metastatic disease or a worse outcome[18].

The treatment of choice is a wide surgical resection, which must include the excision of any involved lymph nodes. Unfortunately, this was not possible in our case, due to the involvement of the thoracic wall. Adjuvant radiotherapy is frequently used when a total excision cannot be achieved or in the case of recurrent disease, which was not considered in our patient due to the extent of the disease and anticipated toxicities, namely lung injury. Chemotherapy is often used in patients with distant metastases, yet in most cases, it does not seem to improve the outcome[18,23]. Immunotherapy with PD-1/PD-L1 inhibitors is being investigated[24]; crizotinib has produced durable responses in ALK-positive tumors[25] and tocilizumab can be used for treating paraneoplastic inflammatory syndrome associated with AFH[26], but these agents still need further research.

Despite starting chemotherapy after the initial surgery, our patient showed rapid disease progression, as well as severe treatment-related complications which precluded the continuation of intensive treatment.

This case, with its rare aggressive presentation and rapid progression, underlines the fact that the correct diagnosis and adequate treatment of AFH remains challenging. A high degree of suspicion from all members of the Oncology multidisciplinary team is needed in a disease whose malignant potential is not yet fully understood.

Author contributions

S.I. de Almeida: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. S. Cochito Sousa: Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. C. Mendes: Conception and design of the study, report, review or other type of work or paper; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. R. Cabrera: Analysis or interpretation of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. A. Lacerda: Conception and design of the study, report, review or other type of work or paper; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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