Evidence of Chemoresponsiveness in Unresectable Metastatic Angiomatoid Fibrous Histiocytoma

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Summary: Angiomatoid fibrous histiocytoma (AFH) is a soft tissue neoplasm of intermediate biological potential. Typically a slow-growing tumor, it can recur locally. Rarely, it manifests as a soft tissue sarcoma capable of metastasis. When metastases are non-amenable to local therapy, it is believed uniformly fatal. We present 3 patients with metastatic AFH who demonstrated a sustained response to chemotherapy; including one who achieved complete remission with cryoablation. These cases reinforce the potential value of chemotherapy in some patients with unresectable metastatic AFH and provide the first case in the literature of cryoablation in AFH.

Key Words: angiomatoid fibrous histiocytoma, chemoresponsiveness, cryoablation

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Angiomatoid fibrous histiocytoma (AFH) is a rare, typically indolent soft tissue neoplasm predominantly involving the deep dermis/subcutis of the extremities or trunk in the adolescent and young adult population (mean age, 15 to 20 y) although may arise in other sites, including retroperitoneum, vulva, ovary, and mediastinum. It can also affect children and older adults.[1–3] Metastatic disease is documented in <5% of patients.[1,4–6] Paraneoplastic inflammatory syndrome (PIS), with systemic symptoms of cytokine release, usually anemia, pyrexia, and weight loss, may be present where the tumor harbors an *EWSR1-CREB1* translocation.[4,5,7–9]

Histologically, AFH is a benign-appearing neoplasm comprising sheets of uniform epithelioid, ovoid, or spindle cells with bland vesicular nuclei and moderate amounts of eosinophilic cytoplasm with minimal cytologic atypia. Immunohistochemistry is variably positive for CD68, epithelial membrane antigen, desmin, CD99, and actin.[1,4,10,11] Behavior is not predictable from histologic parameters, such as the presence of atypia or mitotic activity. The *EWSR1-CREB1* t(22q12)(q33;q12) translocation is found in the majority of cases with *EWSR1-ATF1* t(22q12)(q13;q12) also reported and *FUS-ATF1* t(21q22)(q13;q12) seen in 7% to 10% of cases.[1,12–14]

Surgery is the mainstay of management, with an excellent prognosis when primary complete excision is achieved[5,15] but surgical clearance may not be possible in the setting of metastatic disease. Adjuvant radiotherapy may be considered when excision is incomplete.[16] Local recurrence is rare (2% to 10%) after complete resection.[17] Regional soft tissue or lymph node involvement may occur with local recurrence, with or without distant metastatic disease in the lungs, liver, and brain.[1,6,15]

A previous review found no evidence for benefit of systemic chemotherapy for metastatic disease;[5] however, two subsequent case reports of patients with locoregional recurrence demonstrate chemoresponsiveness.[9,15] We report 3 further cases, which suggest a role for chemotherapy and nonsurgical local therapy options in treating AFH.

CASE DESCRIPTIONS

A 2-year-old girl presented with a 1-month history of a right distal forearm mass, lethargy, and reduced appetite. Examination revealed a 2 cm hard lesion in the medial forearm compartment with overlying bluish discoloration. Magnetic resonance imaging demonstrated a subcutaneous well-circumscribed, heterogeneous, cystic, and solid lesion (13×7×11 mm) characterized by a central vascularized component.

After a biopsy, a wide local excision preserved function in the adjacent neurovascular bundle. Histology revealed AFH with *EWSR1-ATF1* fusion detected by reverse-transcriptase polymerase chain reaction. Chest radiograph was unremarkable. Although medial and deep margins were involved with the tumor, a watch-and-wait approach was taken.

Six months later, she developed a local recurrence with a right axillary lymph node. Reexcision of both achieved apparent clear margins; histology confirmed recurrent AFH in both. A pediatric solid-tumor-specific Next Generation Sequencing (NGS) panel (Version 2)[18] identified no actionable targets. Further staging highlighted an area of uncertainty at the primary site, a lesion in her right upper arm, and bilateral multiple subcentimeter pulmonary metastases.

She was treated with ifosfamide and doxorubicin chemotherapy (Table 1) but when imaging after 2 cycles demonstrated mixed response (right upper/forearm lesions larger; ipsilateral axillary lymphadenopathy, and bilateral lung metastases both decreased in size), she received second-line chemotherapy with cyclophosphamide-based chemotherapy (Table 1). Pulmonary metastases resolved after the fourth cycle of second-line therapy. Local control was achieved with cryoablation of the right forearm and upper arm lesions. She sustained a small skin blister and

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TABLE 1. Cases of Metastatic AFH Treated With Chemotherapy

Case (author)	Age (y)	Fusion	Site of primary disease (including metastatic if present at initial diagnosis)	Site of relapse/recurrence	Signs of PIS present	Treatment	Follow-up
1 (Corley)	2	ESWR1-ATF1	Distal right forearm mass	Local recurrence at right axillary node Metastatic disease in upper arm and bilateral pulmonary metastases	No	Local therapy: wide local excision Primary relapse local therapy: reexcision + lymph node resection with apparent clear margins First line relapse chemotherapy: ifosfamide 9 g/m^2 and doxorubicin 75 mg/m^2 every 21 d ×2 cycles Second line: CAVDo (cyclophosphamide 1500 mg/m^2, actinomycin 1.5 mg/m^2, doxorubicin 30 mg/m^2, vincristine 1.5 mg/m^2) ×3 then VAC ×5 (cyclophosphamide 1500 mg/m^2, actinomycin 1.5 mg/m^2, vincristine 1.5 mg/m^2) Local therapy to relapse sites: cryoablation (primary forearm lesion and metastatic upper arm lesion)	Maintained complete response at 36 mo off treatment
2 (Corley)	22	EWSR1-CREB1	Left popliteal lesion with pulmonary metastases	NA	Yes	First line: ifosfamide 9 g/m^2 ×1 cycle Second line: oral cyclophosphamide 200 mg daily for 7 d ×1 cycle Third line: cyclophosphamide 25 mg/m^2 ×2 cycles Fourth line: single agent paclitaxel ×21 cycles (45 mg/m^2 escalating to 60 mg/m^2; days 1/8/15 every 28 days)	Maintained partial response 24 mo off treatment
3 (Corley)	18	EWSR1-CREB1	Left posterior shoulder	Recurrence at primary site, locoregional axillary lesions and pulmonary metastases	Yes	R1 surgical resection First line relapse therapy: crizotinib 250 mg BD ×2 mo Second line: CAVDo (cyclophosphamide 1500 mg/m^2, actinomycin 1.5 mg/m^2, doxorubicin 30 mg/m^2, vincristine omitted) ×4cycles R0 surgical resection after chemotherapy Doxorubicin was substituted with liposomal doxorubicin (40 mg/m^2) for cardiac toxicity in his third and fourth cycles	Maintained response 18 mo off treatment
4 (Bernini et al)[15]	9	Unknown	Soft tissue mass in left inguinal area with noncontiguous metastatic disease in left sacral ala	Progression of primary tumor (after 6x cycles of chemotherapy)	Yes	First line: Vincristine, cyclophosphamide, actinomycin/alternating with doxorubicin ×8 cycles Local therapy: complete surgical resection of primary with clear margins Postresection treatment: 2× further cycles chemotherapy	Complete response 11 mo off treatment

TABLE 1. (*continued*)

Case (author)	Age (y)	Fusion	Site of primary disease (including metastatic if present at initial diagnosis)	Site of relapse/recurrence	Signs of PIS present	Treatment	Follow-up
5 (Ogden et al)[9]	3	EWSR1-CREB1	Right forearm with antecubital fossa nodes	Local recurrence with metastatic spread to lymph nodes of upper arm and axilla	No	Local therapy: surgical excision with 1 to 2 mm margins Second local therapy: total axillary node clearance (2/25 nodes positive) Relapse treatment: ifosfamide / doxorubicin ×6 cycles	Partial response 2 y off Rx
6 (Pettinato et al)[7]	9	Unknown	Left thigh	Recurrence of primary with regional lymph nodes	No	Local therapy: surgical excision (no detail on margins) Relapse therapy: VAC (cycle number unknown) and radiotherapy	Died of disease at 21 mo
7 (Costa et al)[17]	34	Unknown	Left thigh (delayed diagnosis —lump present for 17 y)	Pulmonary mets (15 mo after excision of primary) Brain mets (19 mo after excision)	No	Local therapy: complete excision of thigh mass Relapse treatment for pulmonary mets: VAC (cycle number unknown) Second line relapse treatment: radiotherapy (for brain metastasis)	Died of disease at 26 mo after original excision
8 (Costa et al)[17]	3	Unknown	Neck	Local recurrence (7 mo after primary chemotherapy) Pulmonary metastases (13 mo)	NA	Local therapy: incomplete excision First line treatment: chemotherapy (after incomplete excision) (no details) Relapse treatment: wide excision (including clavicle) and radiotherapy Second relapse treatment: chemotherapy (no details)	Died of disease at 21 mo
9 (Matsumura)[6]	54	Unknown	Thigh (skeletal muscle)	Pulmonary metastases	NA	Local therapy: wide excision of primary Relapse therapy: chemotherapy (no details) and radiotherapy	Died of disease at 15 mo
10 (Qian)	33	EWSR1 and FUS rearrangement not detected	Buttock	Regional LN (3 mo after resection) Pulmonary metastases (8 mo after resection)	No	Local therapy (primary disease): excision Relapse treatment: chemotherapy (no details available)	Unknown

AFH indicates angiomatoid fibrous histiocytoma; PIS, paraneoplastic inflammatory syndrome.

mporary radial nerve injury, which resolved with conservative management. Imaging a 10-week postcryoablation demonstrated complete remission, and she remains stable on surveillance at 36 months off treatment.

In the second case, a 22-year-old girl, presented with fatigue, syncope, breathlessness, and hemoptysis. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computerized tomography exhibited multiple subcentimeter lung nodules bilaterally; consolidation in the superior segment of the right lower lobe; an ipsilateral apical hyperdense area with low-grade increased ^{18}F-FDG uptake (SUV_{max} 3.3); low-avidity lymph nodes in the right thoracic inlet, ipsilateral infrahilar, hilar, and subcarinal groups (SUV_{max} 5.0). Lung biopsy suggested ANCA-negative vasculitis. She received 4 cycles of pulsed cyclophosphamide, 2 cycles of rituximab, and 1 pulse of methylprednisolone over 6 months with minimal improvement.

A year after the first presentation, she developed a left popliteal lesion; biopsy showed AFH harboring *EWSR1-CREB1* fusion, subsequently excised with clear margins. Computed tomography demonstrated progressive pulmonary lesions (biopsy confirmed metastatic AFH) with hepatosplenic disease and retroperitoneal lymphadenopathy. NGS screening showed no actionable targets.

Initial attempts at chemotherapy (Table 1) were poorly tolerated with neutropenic sepsis, vomiting, and hematological toxicity. Single-agent paclitaxel was elected as the next-line treatment in the setting of poor chemotherapy tolerance and inability to dose escalate (Table 1). She received 21 cycles of paclitaxel with a resolution of disease below the diaphragm after 11 cycles, continuing shrinkage of the pulmonary metastases up to cycle 15, and stable unresectable disease in the right lung for a further 11 months. She elected to come off treatment and has maintained partial response with only 2 post-treatment neoplastic residua, which are stable 24 months off treatment.

Our third case, a previously well 18-year-old obese boy, initially presented at an overseas centre with a localized swelling over his left posterior shoulder and upper lateral chest after significant intentional weight loss. Biopsy demonstrated AFH and he went on to definitive surgery with an R1 resection.

Four months later he became generally unwell with vomiting, weight loss, and anemia (Hb 50 g/dL). He was found to have relapsed with pulmonary metastases and bulky axillary disease and, confirmed on biopsy to be recurrent *EWSR1-CREB1* fusion-positive AFH with ALK over-expression. He was treated with 2 months of crizotinib without objective response, complicated by progressive jaundice, 20 kg progressive unintentional weight loss, and vomiting. He then traveled to our centre for further treatment.

On arrival, he had a Karnofsky performance score of 50, a firm, nontender left axillary mass, significant muscle wasting of bilateral thenar eminences and lower limbs, generalized decreased tone and power (worse in the lower limbs), and severe peripheral sensory neuropathy. He had persistent fevers, ongoing weight loss despite total parenteral nutrition, and transfusion-dependent anemia. Restaging demonstrated bulky axillary disease, associated subpectoral and axillary lymphadenopathy, 2 subcentimeter bilateral ^{18}F-FDG-avid pulmonary metastases and one further indeterminate lung nodule. Bone marrow aspirate demonstrated particulate, hypercellular marrow with hemophagocytosis macrophages, which coupled with elevated ferritin, C-reactive protein, and soluble CD25 led to a presumptive diagnosis of secondary haemophagocytic lymphohistiocytosis; therefore, he was started on high dose steroids as per the haemophagocytic lymphohistiocytosis 2004 protocol.

He responded well to the steroids with initial fever defervescence and proceeded to chemotherapy with cyclophosphamide, doxorubicin, and vincristine (CADo) (Table 1); owing to his significant neuropathy vincristine was omitted. Fevers returned during chemotherapy with steroid wean and interleukin-6 (IL-6) were significantly elevated at 416 ng/L (upper limit of normal <7 ng/L). The patient had an objective radiologic response to treatment, and after his definitive surgery after cycle 4 of chemotherapy, we were able to successfully stop administering steroids.

Surgery was an R0 excision of the upper part of his latissimus dorsi with axillary nodal clearance. Pathology confirmed *EWSR1-CREB1* fusion-positive AFH with 11/26 positive nodes. NGS demonstrated a SMARCA4 variant of uncertain significance but nil actionable variants were found.

Postoperative reassessment imaging confirms complete response including resolution of pulmonary metastatic disease with this response maintained at 18 months off treatment.

DISCUSSION

As surgery is the mainstay of treatment in AFH, metastatic disease is problematic and systemic treatments may be needed to control the unresectable disease. There are only 2 reports in the literature of chemotherapy responsiveness in unresectable AFH; the 3 cases we have presented describing chemotherapy responsiveness in distant metastatic disease further strengthen the evidence for use of systemic treatment in controlling disease and potentially facilitating adequate local control; we have also provided the first description of cryoablation for local control to avoid radiotherapy associated morbidity.

A review of "metastatic" AFH, which included cases with both locoregional disease and distant metastases identified 17 patients (3 females, 11 males, and 3 unknown; range, 3 to 54 y); only 4 survived with no evidence of disease (follow-up, 12 mo to 6 y), all following effective local therapy to the site of recurrence.[5] Three were treated with surgery and 1 with radiotherapy. Five further patients received systemic chemotherapy (details unavailable), none of whom survived.[5]

Two subsequent case reports demonstrate the chemoresponsiveness of AFH.[9,15] A 9-year-old girl with primary left inguinal AFH with a 12 mm metastasis in the left sacral ala was treated with vincristine, doxorubicin, dactinomycin, and cyclophosphamide leading to complete resolution of the distant disease and shrinkage of the primary neoplasm allowing complete surgical clearance.[15] A 3-year-old patient with local recurrence and involved locoregional lymph nodes after borderline excision of the primary forearm mass was treated with ifosfamide and doxorubicin with partial response[9] and remains stable more than 2 years off treatment (B. Pizer personal communication).

There is still a paucity of evidence of chemotherapy choice in these patients. However, the combination of cyclophosphamide, doxorubicin, actinomycin D, and vincristine seems to be an effective treatment based on the response of 2 patients to this regimen and in a previous case report.[15] Paclitaxel was trialed with palliative intent in patient 2 in our series in the setting of poor chemotherapy tolerance and could be an option when chemotherapy is poorly tolerated or when there has been a failure of other treatment lines.

The PIS associated with AFH is thought to be due to excessive IL-6 production resulting from the *ESWR1-CREB1* fusion: CREB1 is a transcription factor, which binds to the IL-6 promoter region. The underlying *EWSR1-CREB1* fusion in patient 3 was the likely cause of his paraneoplastic features.

AFH tumors producing continuous IL-6 are thought to promote tumor growth by autocrine stimulation. Tocilizumab, an anti-IL-6 monoclonal antibody, has been used previously alongside systemic anticancer therapy in the treatment of paraneoplastic syndrome associated with AFH.[8] A child with unresectable metastatic AFH and PIS had a sustained disease response to tocilizumab as

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a systemic anticancer therapy, although the disease recurred once tocilizumab was stopped with a reresponse when it was restarted.[19] An adult patient with an undiagnosed AFH (thought to be a Baker cyst) presented with PIS and symptoms resolved with tocilizumab. The primary lesion was later completely resected.[20] These cases show the potential use of tocilizumab in treating AFH-associated PIS and raise the intriguing possibility that tocilizumab might

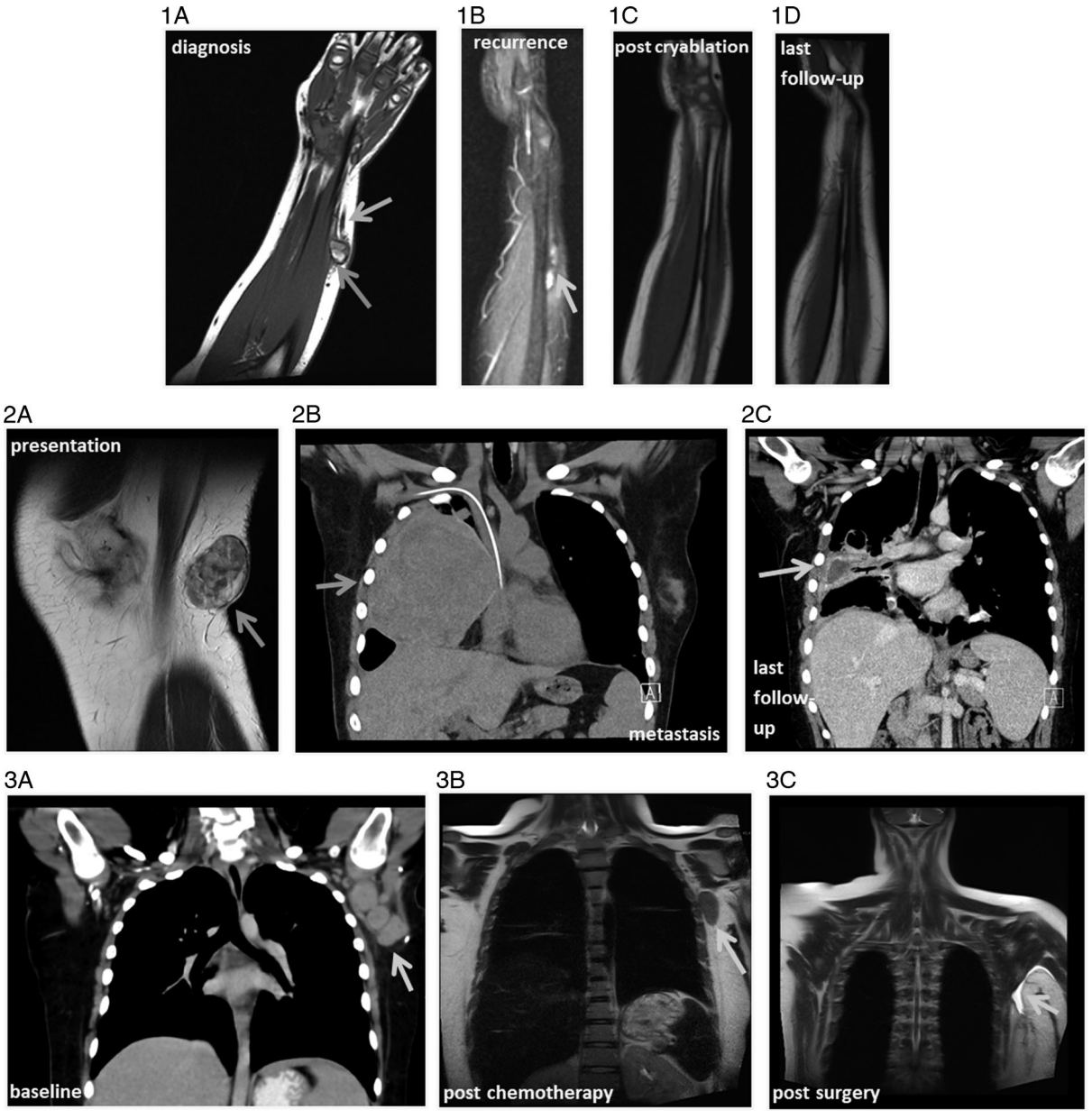

FIGURE 1. CASE 1: 1.A, Magnetic resonance ~~imaging~~ (MR~~I~~) image at presentation. An ovoid well-circumscribed subcutaneous heterogeneous lesion (~~red~~ long arrow) with vascularized solid and fluid components alongside both central and a peripheral rim of blood products; a dominant draining vein (~~lavender~~ short arrow) drained the neoplasm. The mass was intimately related to the lateral surface of the underlying musculature with a small projection into the underlying intermuscular plane. There was perilesional subcutaneous edema. 1.B, Intramuscular recurrence developed at the proximal right forearm surgical bed and in the ipsilateral distal forearm associated with palpable right axillary lymphadenopathy, appreciable on a positron emission tomography/computed tomography (CT) scan as 18F-fluorodeoxyglucose-avid foci. 1.C, ~~MRI image~~ Post-chemotherapy MR examination postchemotherapy and cryoablation. 1.D, Surveillance MR~~I~~ demonstrating complete remission. CASE 2: 2.A, ~~Red~~ arrow—left popliteal heterogenous mass showing a peripheral vascularized rim. 2.B, ~~Blue~~ arrow—CT demonstrating metastatic disease in middle pulmonary lobe. 2.C, ~~Green~~ arrow—shrinkage of all metastases ~~postpaclitaxel~~ post paclitaxel, gradual necrosis, and air changes replaced part of the solid component in the middle lobe mass, which remained stable for 6 months alongside a couple of subpleural nodules in the right upper lobe. Resolution of infradiaphragmatic lymphadenopathy ~~resolved~~ and shrinkage of hepatosplenic deposits. CASE 3: 3.A, Baseline CT at our centre; demonstrated 3 metabolically-active discreet left axillary masses. ~~3.B, Orange arrow—shrinkage of left axillary masses~~ which shrunk (3.B, arrow) after chemotherapy. 3.C, ~~Postoperative~~ Post-operative examination MR~~I~~ demonstrating seromas (~~green~~ arrow), but no residual disease ~~was~~ appreciable at the surgical bed ~~on MRI~~.

induce tumor response in *ESWR1-CREB1* fusion-positive AFH with PIS[19] however, the evidence here is lacking. It is an option to consider in future patients with metastatic disease, especially those with a significant systemic inflammatory response.

None of our patients showed actionable molecular aberrations on NGS sequencing. In this era of personalized medicine, ongoing molecular profiling efforts, such as the UK NHS genomic medicine service and Stratified Medicine in Pediatrics Study (SM-Paeds, ISRCTN21731605), will demonstrate whether actionable targets are sometimes present in AFH. Further understanding of the downstream effects of the gene fusions in the future may direct the use of targeted therapies in rare patients with metastatic disease (Fig. 1).

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