Extra-abdominal recurrent aggressive fibromatosis: A case series and a literature review

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Abstract. Aggressive fibromatosis is a rare clonal proliferative tumor arising from mesenchymal cells in the fascia and musculoaponeurotic structures. The aim of the present study was to describe several cases of extra-abdominal recurrent aggressive fibromatosis. The present study was a single-center retrospective case series of patients with recurrent aggressive fibromatosis. The cases were managed at a single private facility. A total of 9 patients with recurrent fibromatosis were included. The mean and median ages of the patients were 29 and 30 years, respectively. In total, two thirds (66.67%) of the cases were female. A negative previous medical history was reported in 7 cases (77.7%), and diabetes and hypertension were reported in 1 case (11.1%). Overall, only 1 case (11.1%) had a family history of breast fibromatosis. The time interval between primary tumor resection and recurrent presentation was 28 months. In 6 cases (66.7%), the tumor was located in the extremities. Pain was the most common presenting symptom in 6 cases (66.7%). All patients had their recurring tumor surgically removed, followed by radiation in 5 cases. The resection margin was positive in 4 cases (44.4%). Each patient was subjected to a careful three-month follow-up for recurrences. On the whole, the present study demonstrates that despite the fact that several therapeutic approaches for extra-abdominal recurrent aggressive fibromatosis have been described in the literature, there is a significant likelihood of recurrence following resection.

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Introduction

Fibromatosis, also termed desmoid tumor or aggressive fibromatosis (AF), is a clonal proliferative tumor that emerges from mesenchymal cells in the fascia and musculoaponeurotic structures and belongs to a small subset of soft tissue lesions (1,2). It is a rare soft tissue tumor that accounts for ~0.03% of all tumors and <3% of all soft tissue tumors, with a general population incidence of 2-4 per million individuals per year (3). Although the causes of this condition remain unclear, a connective tissue proliferation disease has been proposed as a possible cause. AF in adults has been linked to inherited diseases (Gardner's syndrome), pregnancy (particularly second pregnancy) and female sex hormones. However, these links do not apply to children (4). The majority of the cases are sporadic and genetically linked to Wnt/b-catenin pathway gene mutations, with a smaller percentage related to APC gene mutations (5). Syndromic cases are typically associated with intra-abdominal diseases and familial adenomatous polyposis (6). Regardless of the fact that fibromatosis does not metastasize and has a good survival prognosis, patients suffer significant morbidity as a result of the tumor's invasive progression and the possibility of a high recurrence rate ranging from 15 to 77% (6,7). The aim of the present study was to report a case series of extra-abdominal recurrent AF.

Patients and methods

Study design. The present study was a single-center retrospective case-series of patients with recurrent AF. The present study was approved by the Sulaimani University Ethics Committee (2023/no. 20). All patients or the parents of patients (for cases <18 years old) provided signed consent for their data to be published. The cases were managed at a single private facility. Throughout the previous 7 years (January 2016 to January 2023), the patients were evaluated, treated and followed-up.

Study participants. The socio-demographic and clinical data of the patients were obtained from the electronic health records of the Orthopedic Clinic at Smart Health Tower (Sulaimani,

Iraq), which included age, sex, occupation, previous medical history, previous surgical history, smoking status, family history, radiation exposure history and a histopathological examination (Fig. 1), and details of the characteristics of primary and recurrent tumors.

For histopathological analysis, the sections (5-μm-thick) were paraffin-embedded and fixed with 10% neutral buffered formalin at room temperature for 24 h. The sections were then stained with hematoxylin and eosin (Bio Optica Co.) for 1-2 min at room temperature. They were then examined under a light microscope (Leica Microsystems GmbH).

Inclusion and exclusion criteria. The present study included all patients with extra-abdominal recurrent AF. Patients who do not return for follow-up are excluded from the study. An extensive literature review was performed to identify related articles. Studies published in predatory journals (not properly peer-reviewed) and those with minimal improvement or persistent symptoms were excluded. Predatory journals were defined according to Kscien's criteria (8).

Analysis of patient data. The data were collected and organized using Microsoft Excel 2019. The Statistical Package for Social Sciences 25.0 software (IBM Corp.) was used to qualitatively analyze (descriptive analysis) the data. The data are presented as frequencies, mean, median and range.

Results

A total of 9 patients with recurrent AF were included in the present study. The demographic data and clinical characteristics of the patients with primary tumors are presented in Table I. The patients varied in age from 7 to 60 years of age, with a mean and median age of 29 and 30 years, respectively. In total, two thirds of the cases (n=6; 66.67%) were female. A negative previous medical history was reported in 7 cases (77.7%), and diabetes and hypertension were reported in 1 case (11.1%); migraines were also reported in 1 case (11.1%). The previous surgical history was negative in 4 cases (44.4%), 2 cases had a history of cesarean section (22.2%), 1 case had a history of hemorrhoidectomy (11.1%), and another one had a history of pilonidal sinus disease. Overall, only 1 case (11.1%) had a family history of breast fibromatosis. The upper extremities were the site of primary tumors in 3 cases (33.3%), the lower extremities in 3 cases (33.3%), the chest wall in 2 cases (22.2%) and the lower back in 1 case (11.1%). The most common symptom of the primary tumors was pain at the tumor site (n=8; 88.9%). All primary tumors were surgically removed. In primary resection, the resection margin was positive in 3 cases (33.3%), negative in 2 cases (22.2%) and was undetermined in 4 cases (44.4%). Only 1 case (11.1%) of surgical site infection was reported. Following primary tumor excision, only 1 case (11.1%) underwent radiotherapy. Three cases with a positive resection margin did not undergo adjuvant radiotherapy, and as primary resection was not performed at Orthopedic Clinic at Smart Health Tower for these 3 cases (outpatients), the exact reason for this was not known (patients may have not agreed to this). Another case rejected adjuvant radiotherapy following recurrent resection.

The time interval between the primary tumor and the recurrent presentation was 28 months, ranging from 8 to 84 months. The clinical characteristics of patients with recurrent tumors are presented in Table II. In 6 cases (66.7%), the tumor was located in the upper and lower extremities, in 2 cases (22.2%) it was located in the chest, and in 1 case it was located (11.1%) in the back. Pain was the most common presenting symptom in 6 cases (66.7%), followed by a palpable mass in 3 cases (33.3%). The recurring tumor was completely surgically removed in all patients. The resection margin was positive in 4 cases (44.4%), negative in 2 cases (22.2%) and undetermined in the remaining cases. As regards the post-operative complications of recurring tumor resection, 1 patient (11.1%) had delayed wound healing, 1 patient (11.1%) had a surgical site infection and 1 patient (11.1%) had a femoral nerve injury. Following the removal of the recurrent tumor, 5 patients (55.6%) underwent radiation. Each patient was subjected to a careful 3-month follow-up for further recurrences. The follow-up of the cases revealed a good prognosis in all cases.

Discussion

Under normal physiological conditions, fibroblasts play a critical role in the healing process and the preservation of vital organs, such as the lungs, liver, blood vessels, heart and kidneys; however, when specific cells acquire gene mutations, neoplasms can form, leading to the emergence of AF (9). The World Health Organization (WHO) defines AF as an intermediate soft tissue tumor with clonal fibroblastic proliferation originating from deep soft tissue and the potential to infiltrate locally (2). Fibromatoses are divided into three categories based on anatomic location: Intra-abdominal, abdominal wall and extra-abdominal (10). Extra-abdominal AFs are rare, slow-growing tumors with a varying biological behavior (4). The differentiation between intra-abdominal and extra-abdominal AFs is therapeutically essential due to variations in etiology, biological behavior and morbidity associated with surgical excision (6).

The peak incidence of AF occurs between the ages of 25 and 35 years, with a predominance observed in females (11). The most common symptom is a painless, growing mass; however, symptoms such as neurologic problems, joint stiffness, or gastrointestinal discomfort may also emerge as a result of tumor growth (9). Extra-abdominal head and neck lesions are more aggressive than other extra-abdominal lesions, resulting in significant bone damage and erosion of the base of the skull. They can occasionally expand to the trachea. Extra-abdominal tumors affecting the limbs may cause loss of function as a result of extensive resection, local recurrence and radiation therapy (4). This tumor is recognized as a highly unpredictable tumor with high rates of local recurrence (11). The time to relapse in the initial tumor varies from 8 to 23 months (median, 17.3 months), whereas the time to relapse in the recurrent tumor ranges from 3 to 26 months (median, 14.8 months) (12). In the present study, the female-to-male ratio was 3:1. Pain was the most prevalent presenting symptom in 66.7% of the cases, followed by a palpable mass in 33.3%. The mean interval from primary to recurrent presentation was 28 months.

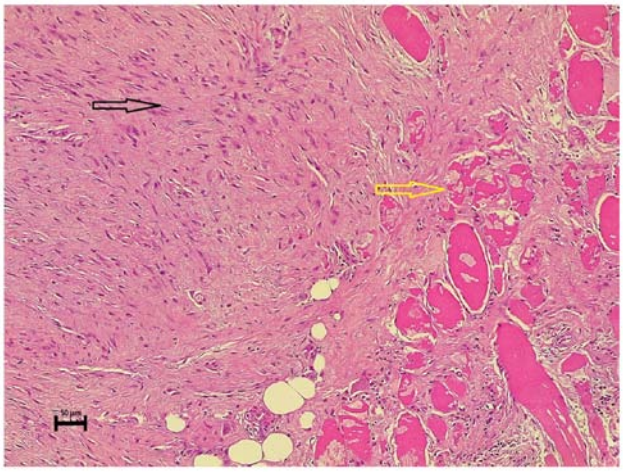

Figure 1. Bland looking spindle cell proliferation (dark arrow) infiltrating to the adjacent skeletal muscle tissue (yellow arrow). Magnification, x400.

Although computed tomography reveals the size of the tumor and its association with the neurovascular systems, magnetic resonance imaging (MRI) is the modality of choice for diagnosing and evaluating the extent of the tumor and the course of the disease following therapy. The features of an MRI vary. Heterogeneous variations are typical, depending on the collagen distribution and cellularity of the lesions. In both T1- and T2-weighted sequences, the lesions may be hypo- or hyper-intense compared to surrounding muscles or adipose tissues, with sharp or poorly demarcated margins (4,13). All patients in the present study were diagnosed and staged using MRI.

In recent years, urgent surgical therapy for extraperitoneal AF has not been recommended. According to the European Guidelines, the 'watchful waiting' strategy is the preferred therapy for asymptomatic AF (9,14). However, as the existence of the tumor is a pathological state in itself, some patients seek surgical therapy even when there are no obvious symptoms or disabilities caused by the tumor. AF can be treated with surgery, radiotherapy or chemotherapy; however, there is limited information available on the selection process for the appropriate treatment for each particular patient (15). In all age groups, full-margin surgical resection remains the treatment of choice for local tumor management. However, the invasive nature of AF renders complete removal difficult without compromising neighboring tissues, resulting in considerable functional impairment (3). Radiotherapy can be a successful therapeutic option, and it can be used as the only treatment for resected tumors with local recurrences, unresectable tumors and in individuals who refuse surgery. Radiotherapy has lately been established as a key therapeutic option for individuals who have relapsed following surgery (16). In the present study, all patients underwent complete tumor resection, followed by radiation in 5 cases.

Non-steroidal anti-inflammatory agents, such as indomethacin or sulindac, have either been utilized as single agents or in combination with anti-estrogens in the treatment of AF, with varying response rates reported based on limited series and case reports (4). Chemotherapy has infrequently been used due to the indolent and non-metastasizing nature of extra-abdominal AF. Agents such as doxorubicin, methotrexate, vincristine, dactinomycin, cyclophosphamide, vinblastine, hormonal therapies and kinase inhibitor drugs have all been documented with varying degrees of efficacy (17). According to a previous systematic review, cryoablation is an appropriate palliative therapeutic option as it is associated with a low risk of complications and delivers a long-term tumor response and symptom alleviation (18). High-intensity focused ultrasound is another therapeutic option that has exhibited immense potential as a treatment option for desmoid tumors. While it may have some adverse effects, it stands out for its precise removal capability and minimal invasiveness (19). However, further investigations are required to prove its effectiveness as a curative method. Furthermore, radiofrequency ablation is a minimally invasive treatment option commonly used to treat a number of benign lesions and unresectable malignant tumors by inserting a fine needle electrode into masses with imaging guidance. This treatment modality has also exhibited promising outcomes in several cases; however, it is associated with several side-effects, such as cellulitis and soft tissue necrosis (19).

To date, the patient's features and therapeutic results of recurrent fibromatosis have not been adequately addressed. In cases with recurrent pathology, surgical excision has been associated with a relatively high risk of re-recurrence of almost 90%, despite the fact that the chance of establishing a clean margin does not vary from the first surgical resection. The surgical margin quality following re-resection is unrelated to the frequency of relapse, presumably due to microscopic residual disease in the surgical bed after the original resection. Along with the high risk of failure, surgery continues to play a role in first-time recurrence; however, it does not appear to provide a meaningful benefit when patients return with subsequent recurrences (20).

Previous research has highlighted age, sex, tumor size, location and the surgical margin as key risk factors for surgical outcomes in patients with AF (21). Some researchers have demonstrated that certain genetic variables may be more predictive of AF recurrence as opposed to the resection margin quality (22). Timbergen *et al* (23) reported an association of the CTNNB1 mutation with surgical outcomes in an analysis of previously published studies and found that the S45F mutation was associated with an increased risk of local recurrence. Garvey *et al* (22) discovered that the 45F mutation was the only risk factor that was statistically predictive of recurrence. Although the S45F mutation appears to be related to a significant recurrence rate, it would be a weaker factor than the tumor site if included in the nomogram (15).

There is much debate over whether surgical resection margins have prognostic value for AF recurrence. Since AF is a very infiltrative tumor, assessing the margin status is relatively challenging (5). The previous study by Cates and Stricker (24) hypothesized that some 'close but negative' margins were definitely positive. They also found that a positive or near-positive (1 mm) resection margin was an independent predictor for local recurrence (24). Two recent studies with large patient populations yielded conflicting results. Zeng *et al* (25) studied patients with AF who had macroscopically complete resection, and found that the R1 resection status was a factor associated with poorer recurrence-free survival. Nevertheless, in the study by Crago *et al* (15), which included the largest cohort of patients with complete macroscopic resection, the margin status was not a predictor associated with recurrence.

Table I. The demographic data and clinical characteristics of the patients with primary tumors.

Patient no.	Age, years	Sex	PMH	PSH	FH	Site	Presentation	Management	Size of tumor (cm)	Resection margin	Residual tumor (R) classification	Complications	Radiotherapy
1	27	F	-ve	-ve	-ve	Left-side chest below axilla	Severe left arm pain	Excision	4	+ve	R1	-ve	-ve
2	30	M	-ve	PNS	-ve	Upper left chest wall	Upper left side chest pain radiating to arm	Excision	8	+ve	R1	-ve	-ve
3	60	F	HTN, DM	C/S, Hemorrhoidectomy	-ve	Medial aspect of right leg	Mild right leg pain and numbness	Excision	9	-ve	Rx[a]	-ve	+ve
4	46	F	Migraine	-ve	-ve	Left hand	Mild left-hand pain, numbness, and weakness	Excision	3	Unknown	Rx[a]	-ve	-ve
5	14	M	-ve	-ve	Breast fibroma	Left paraspinal (lumbar) area	Mild back pain and swelling	Excision	3.4	+ve	R2	Infection	-ve
6	30	F	-ve	C/S	-ve	Right arm	Right arm pain, numbness, and ecchymosis	Excision	8	Unknown	R2	-ve	-ve
7	14	M	-ve	Tonsillectomy	-ve	Left gluteal area	Mild left gluteal pain	Excision	6	Unknown	R2	-ve	-ve
8	7	F	-ve	-ve	-ve	Right gluteal area	Swelling	Excision	N/A	-ve	Rx[a]	-ve	-ve
9	35	F	N/A	N/A	N/A	Dorsal aspect of right hand	Swelling	Excision	N/A	Unknown	R1	-ve	-ve

The age range of the patients was 7-60 years, the mean age was 29 years and the median age was 30 years. [a]Could not be assessed due to fragmentation. PMH, previous medical history; PSH, previous surgical history; PNS, pilonidal sinus; FH, family history; -ve, negative; +ve, positive; HTN, hypertension; DM, diabetes mellitus; C/S, caesarean section; N/A, non-available.

[a]Could not be assessed due to fragmentation.

Table II. The clinical characteristics of patients with recurrent tumors.

Patient no.	Interval between primary and recurrence (months)	Site of tumor	Presentation	Management	Size of tumor (cm)	Resection margin	Residual tumor (R) classification	Radiotherapy	Complication
1	12	Left infrascapular region	Left arm pain	Excision	7.6	Positive	R2	No	Delay wound healing
2	18	Upper left chest wall	Swelling	Excision	4.1	Negative	R0	Yes	Negative
3	30	posterior aspect of right distal thigh and popliteal fossa	Swelling	Excision	N/A	Unknown	Rx[a]	No	Surgical site Infection
4	8	Left hand	Severe left-hand pain, numbness and weakness	Excision	4.5	Unknown	Rx[a]	Yes	Negative
5	12	Left paraspinal (lumbar) area	Mild back pain and mass	Excision	N/A	Unknown	R2	No	Negative
6	48	Right arm	Right arm pain, numbness, and ecchymosis	Excision	12	Positive	R2	Yes	Negative
7	84	Left gluteal area	Swelling	Excision	9.5	Positive	R2	Yes	Femoral nerve injury
8	14	Right gluteal area	Swelling	Excision	4.8	Negative	Rx[a]	No	Negative
9	Unknown	Dorsal aspect of right hand	Painful mass	Excision	5	Positive	R1	Yes	Negative

According to a previous study, the microscopic negative margin state significantly affects the recurrence rate, and the recurrence rate is considerably reduced following full resection with negative margins for both original and recurrent tumors (6). These findings suggest that a full resection is the targeted outcome, and even recurrence rates in patients with a primary tumor are still very low following an R1 resection (6). By contrast, other previous large retrospective studies found no influence of the margin status on recurrence. However, these studies did not distinguish between intra-abdominal and extra-abdominal AF or account for varying adjuvant treatments (26,27). Age is also a significant predictive factor associated with the biological processes of AF. In their study, He *et al* (5) found that younger patients had a greater probability of local recurrence.

The location of the tumor is another factor associated with a greater likelihood of recurrence. It has been previously demonstrated that the extremities are an independent risk factor related to the local recurrence of AF (15). Tsagozis *et al* (20) also discovered that extremity lesions, particularly those of the lower extremities, had a greater probability of recurrence than trunk and pelvic lesions. This may be partially due to the proximity to neurovascular systems and the difficulty in achieving adequate resection margins in such locations (28). The majority of the patients (n=6; 66.7%) in the present study experienced AF of the extremities.

A larger tumor size is another debatable risk factor that has previously been identified. Several researchers have discovered that the size of the tumor increases the likelihood of recurrence (25). However, others have not found such an association (29). According to the study by Wang *et al* (9), a larger primary tumor size was related to a higher likelihood of recurrence and a shorter time to recurrence. Additionally, as larger lesions tended to infiltrate adjacent vessels and nerves, the lesion was not removed completely during surgery in order to protect local tissue function, and some tumor cells remained in the surrounding tissue, resulting in a short-term recurrence (9). Another study discovered that tumor size (5 or >5 cm) had a substantial effect on recurrence (10).

Adjuvant radiotherapy is a controversial subject in the treatment of AF since earlier research findings vary; some studies have found that radiation is related to improved local control of AF (25,30), while other scholars have found no effect (15). According to a previous study, adjuvant radiation appears to minimize the incidence of local recurrence following surgical resection with positive resection margins (6). Its efficacy in minimizing local recurrence is particularly prominent following the R1/R2 resection of recurrent AF and appears to have no additional benefit when surgical resection is complete at the time of the histological analysis (6). Guadagnolo *et al* (31) studied patients with primary and recurrent AF in whom adjuvant radiation obtained a 10-year local control rate of 78%. In their systematic review, Yao *et al* (32) concluded that surgery plus adjuvant radiation decreased recurrence compared to surgery alone. Adjuvant radiation was thus suggested for all patients, even those with negative resection margins (32). Radiotherapy with doses ≥60 Gy has been demonstrated to enhance local control rates by 80 to 88% (31).

Moreover, several studies have found that radiation efficacy is associated with margin status (6,33,34). A previous study found that in patients with positive margins, post-operative adjuvant radiation enhanced local control and lowered the recurrence rate compared to surgery alone (33). A previous meta-analysis found that although adjuvant radiation was not effective for patients with negative margins, it may enhance local control and prevent recurrence in individuals with inadequate resection (6). The National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant radiation for patients with R1 resection and definitive radiotherapy for those with R2 resection (34). The apparent limitations of the present study were the small sample size, the lack of a genetic profile of patients to identify the role of genetic factors in disease emergence and the lack of any explanation regarding the etiology of the cases.

In conclusion, fibromatosis is a rare, locally invasive fibroblastic tumor with no metastatic potential. Despite the fact that several therapeutic approaches have been described in the literature, there is a significant likelihood of recurrence following resection. Further studies are thus required to further determine the management and risks of recurrence.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SKA provided major contributions to the study concept and the final approval of the manuscript. FHK and MNH were involved in the literature review, in the design of the study, and in the writing of the manuscript. AMA was the histopathologist who examined the specimen. SAA, SHT, CSO, RJR, FHF, BAA and SHM were involved in critically revising the manuscript and in data interpretation. All authors have read and approved the final manuscript. SAA and SKA confirm the authenticity of all the raw data. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent

The present study was approved by the Sulaimani University Ethics Committee (2023/no. 20). All patients or the parents of patients (for cases <18 years old) provided signed consent for their data to be published.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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