Recurrence Patterns and Management Options in Aggressive Fibromatosis

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Abstract Aggressive fibromatosis is a rare neoplasm arising from musculoaponeurotic structures. Our aim is to share our experience with this rare tumor in our institute and to discuss the more perplexing recurrence patterns and the management options. This is a retrospective study of the disease, treated in our institute for the past fourteen years. A total of 36 patients were analyzed. The demographic pattern of the disease, various treatment modalities offered and their outcome along with patterns of recurrence were studied. Our study showed a demographic pattern mostly similar to the rest of the world. But the pattern of recurrence and the multicentric and the non-random pattern of presentation observed in our study showed some difference from the other studies. We suggest surgery as the primary modality with radiation reserved for select patients with margin positivity, inoperable tumors, and multiple tumors. Since the disease has a long natural history a wait and watch policy can be observed for giving adjuvant RT. There is need for prospective multi-institutional RCTs to shed light on the unknown facts about this disease.

Keywords Fibromatosis · Recurrence patterns · Surgical excision · Adjuvant · Radiotherapy · Tamoxifen

Synopsis: We suggest surgery as the primary modality with radiation reserved for select patients

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Introduction

Aggressive Fibromatosis also known as “Desmoids” is a group of clinically diverse deep-seated fibrous neoplasms [1]. It is a relatively rare neoplasm constituting less than 3% of all soft tissue tumors with an incidence of 2–4 per 100000 population [1–5]. It is a locally aggressive tumor with a high rate of recurrence but with no tendency to metastasize [6]. Factors influencing such a high rate of recurrence and the pattern in which it recurs are not similar in various studies. Surgery is the primary modality of treatment. But, due to their enigmatic recurrence pattern, adjuvant and salvage modalities of treatment for this disease are not optimized. In this article, we will be discussing our 14 year experience with this relatively rare tumor and the recurrence patterns and treatment strategies we offered.

Patients and Methods

We made a retrospective analysis of 36 patients treated over the past 14 years (1998–2011). This included patients with extra-abdominal, abdominal and intra-abdominal fibromatoses. By analyzing the various data, we obtained information regarding demographic patterns, various surgical therapies offered. Special attention was paid while collecting data regarding the recurrence patterns, salvage modalities, and adjuvant offered, as they are the most intriguing aspect of this disease.

Findings

There was a slight female preponderance in the ratio of 1.25:1 (20 female patients vs. 16 male patients). In children, the disease is very rare and has a male preponderance. We had 5

patients within the age group of 12 and below (13.8%) and 4 of them were male. Mean age at presentation was 27 years (range 7 to 64). The number of tumors at presentation in a single patient ranged from 1 to a maximum of 6 with a tumor size ranging from 3 cm to 20 cm, with an average size of 8.8 cm. 23 were primary tumors and 13 were recurrent. The duration of presenting symptoms was more with recurrent tumors since late recurrence is a common phenomenon in this disease.

There were 31 cases of extra-abdominal, 4 cases of intra abdominal and a case of abdominal fibromatosis (based on Enzeinger & Weiss Classification), in our study. Within the intraabdominal group, we have not encountered any case of mesenteric fibromatosis associated with Gardner's syndrome as shown in the Fig. 4.

Most of the cases of extra-abdominal fibromatosis occurred at sites in and around the shoulder and pelvic girdle, as shown in the Table 1.

Management

After discussion in multidisciplinary tumor board, patients were offered surgical excision as primary modality for tumors that were operable (31 patients) and radiotherapy or systemic therapy for inoperable tumors, those with margin positivity and recurrent tumors on an individual basis after discussion in tumor board. Tumors with inconclusive biopsy results were operated on after considering clinical and radiological features. Surgery was done following adequate oncological principles but consideration was given for preservation of function (Figs. 1, 2 and 3).

The mean tumor size of the surgical group was 8.1 cm. Limb Salvage was possible in all but one patient with involvement of extremities. One patient with attempted limb salvage with vascular reconstruction using a PTFE graft underwent an above knee amputation in the early postoperative period

Fig. 1 Pre operative photo

Fig. 2 Intraoperative defect

following graft failure secondary to infection. Procedures undertaken were shown in the Table 2.

Patterns of Recurrence

There were 14 recurrences (45.2%) which were surgically salvaged. Various variables taken up for analyses of recurrences are given in Table 3.

In the surgical group there were 5 positive margins and 1 close margin. Median follow-up time in our series is 5 year. Four patients were offered adjuvant radiation as per tumor board decision.

Adjuvant Therapy

Four patients received adjuvant Radiotherapy out of which 1 experienced recurrence which was surgically salvaged.

Fig. 3 Post operative picture

Fig. 4 Incidence of intraabdominal fibromatoses in our study

Radiotherapy was given for cases with margin positivity, multiple tumors or multiple recurrences.

Adjuvant tamoxifen was given to 5 patients. Usually it is reserved for inoperable tumors and select patients with margin positivity. One patient with mesenteric fibromatosis has stable disease for the past 5 years with tamoxifen alone and another patient is on follow up 1 year after starting therapy. Three patients on adjuvant therapy were lost for follow up.

Discussion

On comparison of our findings with the World literature, we could find concordance in most of the variables barring a few. There were more boys in the pediatric age group. Only one patient—a young girl was found to have abdominal fibromatosis in contrast to World literature in which fertile females dominate. These, we think, might be due to small number of cases analyzed, but could also be due to different demographic trends in this part of the country.

Surgery was the mainstay of therapy for all operable cases of fibromatosis. This is confirmed in almost all the literature we reviewed. We did not offer adjuvant RT routinely to all patients because of the young age of the patients at presentation and considering the long term complications

Table 1 Site distribution of Extra-abdominal fibromatosis

SITE	Number of cases
Shoulder	4
Arm	9
Forearm	2
Loin	1
Gluteal	3
Leg & foot	3
Head & neck	2
Lower limb	2
Thigh	5

Table 2 Procedures undertaken were shown in the table below

Surgical procedure	No of patients
Wide monobloc excision	21
Scapulectomy	4
Wide local excision & centralization of ulna	2
Wide local excision with excision of metatarsals & bone grafting	2
Laparotomy and excision	1
Amputation	1
TOTAL	31

of radiation in this group of patients. Since the role of anti-estrogens and cytotoxic agents is not very clearly understood in the adjuvant setting they are not routinely used except in select circumstances.

Recurrence

In our analysis, we found sex, site, size, multiplicity at presentation had no influence on recurrence while recurrence at presentation (56% recurrent vs. 24% primary) and positive margin (66% positive margin vs. 10% free margin) had a strong association with recurrence.

The propensity of aggressive fibromatosis to locally recur is related to its infiltrative nature, which makes it difficult for the surgeon to grossly identify the true extent of disease. These tumors lack a pseudo capsule and display nonpalpable diffusion along muscle bundles and fascial planes. This may justify the high recurrence rate of the disease after adequate surgery. Posner et al., Goy et al. and Spear et al. identified positive resection margins as the most important Independent predictive factor of local recurrence [6–9]. But in a study by Merchant et al. [4] and in few other studies positive margin does not affect the outcome adversely. Gronchi et al. [18] speculates that the recurrence rate highly depends on inherent characteristics of the disease, which might be more or less aggressive on its own, so that it might recur or not rather independent of the quality of surgery.

In Gronchi et al's series [18], patients with large tumors located at the extremities or girdles had a higher risk of recurrence, regardless of whether they were excised with positive or negative resection margins. We did not find any such association between site and recurrence.

Unfortunately, there are relatively few large series that outline the actuarial local recurrence free survival rates stratified by microscopic margin status for patients treated by surgery alone. Comparison of local recurrence-free survival rates following surgery in Desmoid tumors is shown in Table 4: [10]

The experience of these institutions suggest that local control rates for patients who are treated by surgery alone

Table 3 Comparison between recurrent and disease free group

		Disease free group	Recurrence group	Time taken to recur (months)
No. of Patients		25	6	
Site		Not significant	Not significant	
Size (cm)		9	9.5	
Median Age (years)		29	35	
No. of primary tumor	Single	22	4	16
	Multiple	3	2	13
Margin Status	Positive	2	4	15
	Negative	23	2	11
Presentation	Primary	16	2	13
	Recurrent	9	4	16

is in the order of 50% when R1 resection is made compared to approximately 75% with R0 resection.

The most intriguing aspect of our recurrence pattern is the time to recur. Although positive margin in our series was associated with high recurrence rate, the duration taken for the tumor to recur in both the positive margin group and negative margin group did not show any significant difference. The number of tumor at presentation, single vs. multiple and the presentation, primary vs. recurrent, also did not show any significant difference in the time taken to recur. Although we could not find any literature evidence to support this fact, we believe this fact reiterates that recurrences in fibromatosis may be more influenced by the biology of the disease (Table 5).

Pattern of Recurrence

Pattern of recurrence in fibromatosis can also be quite different from other tumors. Recurrences can be within the surgical field and also away from it. The recurrence of the tumor away from the field of surgery, more proximally within the same myotome was not classically observed in our series. In our series one patient who had a tumor in the origin of corachio brachialis after surgical excision experienced recurrence at lower end of the muscle about 10 cm away from the primary tumor and subsequent recurrence in

pectoralis major muscle. Here the recurrence pattern is first distal to the index lesion and then proximal to it within the same myotome. Whether this is due to intra muscular microscopic infiltration of the tumor along the muscle spindles or a genetic field defect in the affected muscles is unknown. In few patients the recurrences can be just outside the radiation field. One of our patients experienced a recurrence just outside the radiation field.

Multicentric Fibromatosis –A New Entity

Fong et al. has described an entity where multiple lesions are found typically confined to one anatomical region of the body [11]. In most cases the second growth is found

Table 4 Comparison of local RFS after surgery in various institutions

Institution	No of patients	Follow-up (months)	Local RFS	
			R0	R1
Massachusetts General Hospital	51	12–59	77	56
MDACC	122	113	73	46
MSKCC	128	88	86	49
Govt Royapettah Hospital	36	60	90	44

Table 5 A table comparing our data with the western literature is shown below

Variables	Our study	World literature
Mean Age	27	25–35
Sex (F:M)	1.25:1	1.6:1
Children	13.8(%)	
Sex ratio(F:M)	1:4	1:1
Tumor		
Number	6	
Size	8.8 cm(3–20)	
Site distribution		
Abdominal	2.8%(1)	25%
Extra-abdominal	86.1% (31)	50%
Intra-abdominal	11.1%(4)	15%
Recurrence		
No of recurrence	45.2%(14)	
Margin positive cases	66% (4)	60%
Recurrence after		
Primary surgery	30%	
Recurrent surgery	56%	

proximal to the first growth. This is found in 5% of the patients diagnosed to have extra abdominal fibromatosis.

Although multicentre fibromatosis confined to one anatomical region is a known entity, we describe a new hitherto undescribed non random pattern of distribution of multicentric extremity fibromatosis.

Two male patients presented with multiple fibromatosis of lower limb distributed in gluteus muscles, quadriceps, muscles of popliteal fossa and a lesion in between metatarsals in the foot. One patient underwent wide excision of all lesions in a staged manner and is now undergoing treatment for recurrence at two places (left Thigh and popliteal fossa). The other patient, who has had the disease for the past 10 years, refused any form of treatment. In both patients the tumors were around the hip and knee joint and both of them had the disease for more than 10 years. Fong et al's [11] observation of second growth arising proximal to the first one was not seen in both patients. The new lesions arose both proximal and distal to the index lesion.

One female patient had multiple lesions in the upper limb distributed along Pectoralis major, Biceps, Coracobrachialis and between the metacarpals. These tumors were found arising around the shoulder and elbow joint and again the new lesions arose both proximal and distal to the index lesion.

In all the three patients the lesions were separated widely and found to cross the joints as well. This fact rules out the possibility of skip metastasis or a contiguous spread from the index lesion. The nonrandom pattern of distribution especially the tumors arising between the metacarpals and metatarsal is striking and is not possible with any known local infiltrative patterns.

We believe the muscle groups involved in this form of fibromatosis acquire a genetic defect and some other environmental or hormonal factor makes the tumors manifest itself at a later age. Further studies on these patients may open new avenues in epidemiology.

Adjuvant Therapy

Four of our patients received adjuvant RT out of which 1 experienced recurrence which was salvageable by revision surgery. Recommendations for adjuvant radiation have not been standardized. Interpretation of the limited literature in the use of EBRT in the management of Desmoid tumors is hampered by the rarity of the lesion and the absence of margin-specific actuarial local recurrence rates for large series of consecutively treated patients.

Even though some groups give adjuvant radiation [12–14] to all postoperative patients irrespective of margin status, we followed the policy of giving radiation to only those patients who are margin positive, multiple tumors and recurrent tumors. The reason is that RT does not guarantee

high local control and the young patients we treated might still be salvaged by RT should recurrences occur later.

We offer Tamoxifen to all inoperable tumors [15–17]. One of our patients with mesenteric fibromatosis is having stable disease for the past 5 years. We could not come to any conclusion on the efficacy of tamoxifen since three out of patients are lost for follow-up. We also offer tamoxifen in adjuvant setting for patients who had experienced multiple recurrences. The efficacy of tamoxifen in adjuvant setting could not be analyzed in our series as the number is very small. We are yet to find a clinical situation in which cytotoxic chemotherapy can be considered. The data substantiating the role of endocrine, cytotoxic and NSAIDs are mostly retrospective or non-randomized single institution studies.

Conclusion

Aggressive fibromatosis is an enigma occupying the twilight zone between benign and malignant behavior. From our Institute's experience we conclude that recurrence in fibromatosis is atleast partly independent of management options and depends on the inherent biology of the tumor. We suggest surgery as the primary modality with radiation reserved for select patients with margin positivity, inoperable tumors, and multiple tumors. Since the disease has a long natural history, a wait and watch policy can be offered in select patients for giving adjuvant RT since new lesions could arise away from the field of surgery. Myotomic and non-random patterns of recurrence could also be reasons.

The paucity in number of international studies with adequate follow-up might be due to the rarity and the slow growing nature of the tumor. There had never been a randomized controlled study comparing different treatments and recurrence patterns undertaken anywhere in the world. Multi-institutional prospective RCTs and subsequent pooled data analysis may optimize the treatment protocol for this enigmatic and rare disease.

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