

Fibromatosis of the Breast After Mammary Prosthesis Implantation

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Fibromatosis is a locally aggressive tumor accounting for 0.03% of all neoplasms.¹ Fibromatosis of the breast is exceedingly rare and clinically it may mimic breast cancer. We report a case of fibromatosis arising 3 years after implantation of a saline breast prosthesis. We also provide a review of the literature, including information from 11 prior reported cases.

Case Report

A 30-year-old woman was evaluated for a suspicious left-sided anterior chest wall mass. Her history was significant for bilateral breast saline implants 3 years prior, followed by surgical revision 26 months later. Three months following this revision she developed a progressively enlarging, nontender mass along the anterior axillary line, adjacent to the left breast implant. She did not have any known family history of malignancies or familial syndromes, including breast or ovarian cancer or familial adenomatous polyposis (FAP). Bilateral diagnostic mammography did not identify a discrete mass in the area of the palpable abnormality. Magnetic resonance imaging (MRI) was significant for a suspiciously enhancing $5.8 \times 4.3 \times 3.0$ cm mass arising from the pectoralis minor muscle along the posterior superior margin of the breast implant; the superior margin of the mass was irregular and the posterior margin appeared to involve the intercostal muscles (Figure 1).

Core needle biopsies of the lesion were suggestive of fibromatosis versus a low-grade fibrosarcoma versus

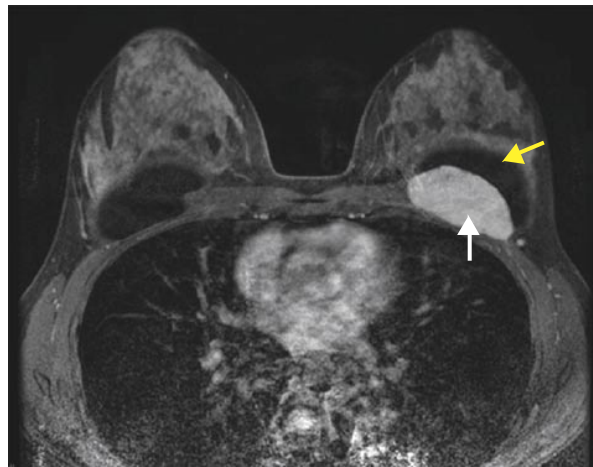


Figure 1. Magnetic resonance imaging (T1 axial image with contrast) showing prosthesis (yellow arrow) and chest wall involvement with fibromatosis (white arrow).

reactive fibroblastic proliferation. Staging positron emission tomography (PET) and computed tomography (CT) scan showed a large, moderately hypermetabolic, soft-tissue density mass within the left chest wall with a standardized uptake value of 2.7; the mass was deep to the pectoralis muscle with slight indentation of the underlying pleura but no destruction of the underlying rib (Figure 2). Given the suspicious imaging findings and the false negative rate associated with needle biopsies, an incisional biopsy was performed. The pathology was consistent with fibromatosis. One week later, the patient underwent total resection of the mass and left pectoralis muscle in conjunction with removal of the bilateral breast implants, chest wall reconstruction using

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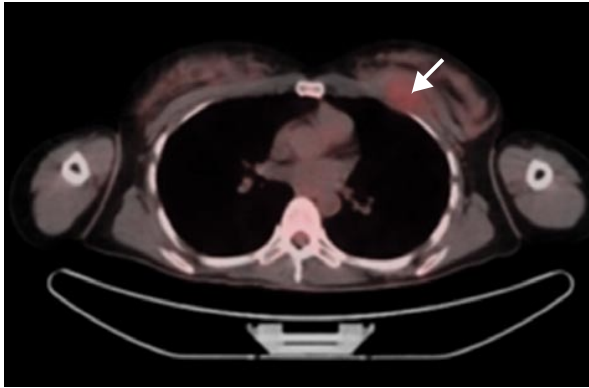


Figure 2. Positron emission tomography/computed tomography scan showing a moderately hypermetabolic (standardized uptake value 2.7) soft-tissue density mass (arrow) involving the chest wall.

methyl methacrylate, and breast reconstruction using an ipsilateral latissimus dorsi musculocutaneous flap (Figure 3). Gross sectioning of the surgical specimen identified a $6.0 \times 5.0 \times 2.5$ cm mass inside the capsule of the breast implant, and histologic review confirmed the diagnosis of fibromatosis (Figure 4) with widely clear surgical margins and no evidence of extension to bone. After successful surgery, she made a full recovery and is in regular follow-up.

Discussion

Fibromatosis has been described under various names including desmoid tumor and aggressive fibromatosis. It is a rare tumor, with an estimated 900 new cases diagnosed each year in the United States; it accounts for less than 3% of all soft-tissue tumors.¹ It is a benign, but locally aggressive, neoplasm that presents a problem in recognition and management because of the striking discrepancy between its deceptive histologic appearance with infiltration of the

surrounding soft tissues, and its propensity towards local recurrence. Unlike malignant tumors, fibromatosis does not metastasize and is infrequently associated with disease-specific mortality.²⁻⁴

These tumors occur between the ages of 15 and 60 years, with the median age of diagnosis in the early 30s. There is a 2-to 3-fold predominance of these lesions in women.⁵ Fibromatosis can occur in a variety of anatomic locations and can be broadly divided into abdominal and extra-abdominal lesions, with shoulder (21%), anterior/posterior chest wall (17%), and thigh (13%) being the most frequent locations.⁶ In most cases, the lesion is firm and fixed to surrounding tissue, presenting as a poorly circumscribed mass that has grown insidiously.

The strongest predisposing factor is the diagnosis of FAP and, more specifically, Gardner syndrome, which is distinguished by the presence of extraintestinal lesions, such as fibromatosis, osteomas, and cysts. In patients with FAP, the estimated risk of developing fibromatosis is 4–20%.^{2,3,7-9} Most cases involve the abdomen,¹⁰ and 68% of such cases occur in the setting of prior abdominal surgery.¹¹ FAP and Gardner syndrome share mutations at chromosome 5q21-22, the locus for the adenomatous polyposis coli (*APC*) gene. More than 300 mutations have been described for the *APC* gene, whose gene product appears to play a role in regulating beta catenin. Although the exact relationship is not completely understood, these mutations are associated with dysregulated beta catenin, and in a preclinical animal model, with loss of degradation of beta catenin–induced development of fibromatosis.¹² In addition, trisomies for chromosomes 8 or 20 have been reported in approximately 20% of cases of sporadic fibromatosis.¹³⁻¹⁵ Of interest, some reports suggest that fibromatosis associated with trisomy 8 is at increased risk of subsequent local recurrence.^{14,16} When compared with other soft-tissue tumors, gene array expression profiling studies have identified distinct patterns inclusive of fibromatosis. In one array study, fibromatosis, leiomyosarcomas, synovial sarcomas,



Figure 3. (A) Intraoperative photograph demonstrating the fibromatosis; (B) tumor specimen after resection.

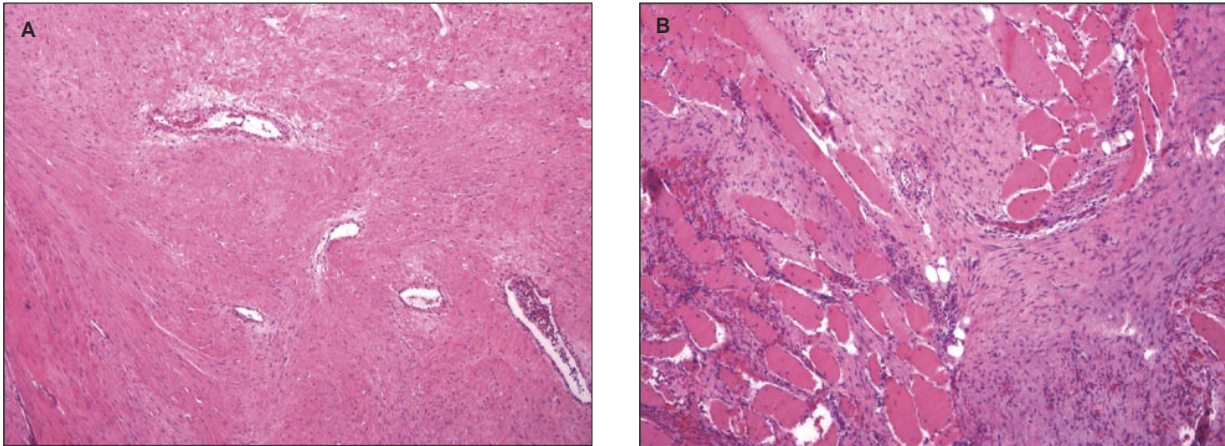


Figure 4. Histopathologic appearance of surgical specimen. (A) A bland spindle cell proliferation arranged in fascicles and showing the characteristic thin-walled vessels; (B) specimen showing invasion and isolation of nonatrophic skeletal muscle fibers by spindle cells.

liposarcomas, schwannomas, and gastrointestinal stromal tumors were found in the same cluster.¹⁷

One possible etiology of fibromatosis is trauma from prior surgery. A history of antecedent trauma is present in nearly 30% of all cases^{18,19} (ie, both sporadic cases and those associated with FAP, irrespective of location). It is often difficult to distinguish recurrent fibromatosis from scar tissue resulting from prior surgical excision. Histologically they display pseudoencapsulation and infiltration of the adjacent tissue structures. Proliferation consists of elongated, slender, spindle-shaped cells of uniform appearance surrounded by and separated from one another by abundant collagen, with little or no cell-to-cell contact.²⁰ There is characteristically sparse cellularity, few mitoses, and rare necrosis. This characterization explains why fine-needle aspiration of these lesions often fails to confirm a diagnosis. The periphery of the lesion often infiltrates the adjacent muscle tissue, and remnants of striated muscle fibers are frequently entrapped and undergo atrophy, which may occasionally be mistaken for malignant change.

Local Therapy

Treatment of fibromatosis is indicated when there is imminent risk to the adjacent structures, for symptomatic lesions, or for cosmesis. The primary treatment is surgical, but radiation therapy is considered if surgery will be unacceptably morbid. Although excellent local control is usually achieved with surgery alone, recurrence rates between 23% and 39% have been reported.²¹⁻²⁵ There are conflicting data on the importance of a complete resection with widely clear margins. Some series report that

the risk of recurrence is independent of margin status,²⁶⁻²⁹ whereas others demonstrate high recurrence rates with close or positive margins.^{21,22} Furthermore, successful salvage therapy for locally recurrent disease is possible in a vast majority of cases. This finding has led to the opinion that patients may be followed by observation alone regardless of margin status.

There are conflicting reports on the benefit of adjuvant radiation in terms of local control rates,^{25,26} and, as noted earlier, there is no clear association between margin status and the risk of recurrence.^{26-30,32} In addition, salvage radiation therapy is usually successful in cases of recurrent disease.^{21,22,33} Therefore, adjuvant radiation therapy is generally not recommended in the setting of clear surgical margins.²³ Though its role in patients with close or positive margins is debated, this therapy should be considered in certain cases in which a relapse might lead to increased morbidity.

For cases in which primary surgical resection is not possible, radiation therapy is an effective therapeutic option. Long-term control is seen in 70–80% of cases treated with radiation alone.^{23,25,29-31} Fibromatosis is slow to respond to radiation, so maximum regression may not manifest for several years.³¹ The optimal radiation dose is between 50 and 60 Gy, administered in 1.8–2.0 Gy fractions over 6–7 weeks. Higher radiation doses do not seem to increase the response but do lead to increased toxicity.²⁹

Systemic Therapy

The mainstay of treatment for fibromatosis is local; however, systemic therapy may be considered if surgery

or radiation proves difficult or ineffective.³⁴ Systemic agents can be broadly characterized as cytotoxic, cytostatic, or biologic. Cytotoxic therapy can be considered for symptomatic patients or those with rapidly growing tumors, whereas cytostatic agents are often used in non life-threatening situations. The data on treatment efficacy are limited to case reports or small case series as opposed to phase II or III trials. Therefore, the lack of sufficient patient numbers and randomized trials does compromise the validity of the reported results.

Cytotoxic agents are usually given in combination, although single-agent doxorubicin has been used.³⁵ The most commonly reported regimens include methotrexate with a vinca alkaloid (vinblastine or vinorelbine); doxorubicin with dacarbazine; doxorubicin with cyclophosphamide and vincristine; and actinomycin-D–based chemotherapy.³⁶⁻⁴⁴ For example, 30 patients received weekly methotrexate (30 mg/m²) and vinblastine (6 mg/m²) for a median interval of 1 year; 80% of these patients had recurrent disease and prior treatment with surgery, radiotherapy, tamoxifen, and/or anthracycline-based therapy, and there was a 60% rate of stable disease and a 40% rate of partial response (PR) with a 10-year progression free survival (PFS) of 70%.³⁶ Another smaller study with 8 patients demonstrated symptomatic relief and minimal toxicity with the same low-dose treatment regimen.³⁷ In refractory cases, however, more aggressive systemic therapy is often warranted. These more aggressive regimens are anthracycline-based with doxorubicin.^{40-43,45,46} For example, doxorubicin (60–90 mg/m²) in combination with dacarbazine (750–1,000 mg/m²) led to responses in 6 of 9 evaluable patients.⁴⁰

The different cytostatic agents with reported activity against fibromatosis include hormonal agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and interferon alpha (IFN α). Much of the interest has been focused on tamoxifen either alone or in combination with an NSAID. Case reports describe PR or stable disease in approximately 65% of patients for up to 12 years with tamoxifen (or toremifene), but large confirmatory studies are lacking.^{34,47} In terms of combination therapies with tamoxifen, a response rate of 70% was reported in a series of 25 patients treated with tamoxifen (120 mg daily) and sulindac (300 mg/day).⁵ Other hormonal agents such as raloxifene (Evista, Eli Lilly), testolactone, and progesterone have also been used effectively, although the optimal dose and duration of treatment remain unresolved.⁴⁷⁻⁴⁹

NSAIDs can be used alone in the treatment of fibromatosis, and most of the studies have involved single-agent sulindac. In one study of 14 patients, sulindac (300 mg daily) was associated with the following rates of response: 7% CR, 50% PR, and 28% with stable disease⁸; the duration of response was not reported. Other groups

have used indomethacin and colchicine with varying success.^{5,50,51} Regarding the efficacy of IFN α , 22% CR and 22% PR rates have been reported, and approximately 56% of patients achieved prolonged disease stabilization.^{52,53}

Novel biologic agents may also have utility in the treatment of fibromatosis. Imatinib (Gleevec, Novartis), a small molecule inhibitor of the BCR-ABL tyrosine kinase, has been the most promising agent thus far. The largest phase II study included 51 patients who received imatinib 300 mg twice daily. Of the 45 evaluable patients, 36 (80%) reached the primary endpoint of either CR or PR at 2 months or stable disease or better at 4 months.⁵⁴ The median time to treatment failure was 6.8 months (95% confidence interval 5.8–17.1). Another phase II trial used a treatment regimen of 400 mg daily; there were 22 evaluable patients out of 40, and an 81% response rate was demonstrated at 3 months (including 1 CR). The dose of imatinib was increased to 800 mg daily upon disease progression, and 2 of 5 patients achieved stable disease.⁵⁵ Due to the long natural history of fibromatosis, longer follow-up is necessary to determine the true efficacy of imatinib in this patient population.

Clinical Presentations

Fibromatosis of the breast can either arise primarily in the breast tissue^{56,57} or invade the breast from the musculo-aponeurotic structures of the underlying pectoralis major muscle. There have been just over 100 cases reported in the literature.⁵⁶⁻⁶¹ It presents as a mobile, firm, typically unilateral, painless breast mass. It is important to define the site of origin, as lesions arising from the musculo-aponeurotic layer have a higher incidence of local recurrence. The recurrence rate is reported to be between 21% and 27% for primary breast fibromatosis and 57% if the tumor arises from the musculo-aponeurotic layer.^{56,57,59} Recurrence of primary breast fibromatosis is seen mostly within 2 years of the initial resection, but recurrences have been reported up to 6 years later.

Radiographically, fibromatosis of the breast may be mistaken for carcinoma by routine mammography because of its irregular shape, high density, and spiculated appearance. These tumors are rarely associated with calcifications. On ultrasound, fibromatosis will appear as an irregular, hypoechoic mass with posterior acoustic shadowing,^{62,63} these findings are indistinguishable from other solid tumors of the breast. CT scans are also of limited use because these tumors have similar attenuation to muscle on CT. MRI is therefore the most useful tool. Although nonspecific, the lesions may be hypointense or hyperintense relative to surrounding muscle on T1- and T2-weighted sequences, and heterogeneous changes are common.⁶⁴⁻⁶⁶ MRI is especially useful for assessing the

Table 1. Review of Previously Published Cases of Fibromatosis of the Breast Related to Breast Prosthesis

First Author (year)	Age, years	Prosthesis Material	Period between implantation and diagnosis	Size of tumor	Treatment	Prosthesis Management	Status after excision
Jewett ST (1979) ⁶⁷	54	Saline	2 years	3 cm	Excision	Removed	Recurrence-free for 8 months
Rosen PP (1989) ⁵⁸	35	Saline	Several years	NR	Excision	Removed	Recurrence 7 months later
Schuh ME (1994) ⁶⁸	41	Silicone	2 years	6.5 cm	Wide Excision	Replaced	Recurrence-free at 3 years
Schiller VL (1995) ⁶⁹	66	Silicone	NR	13 cm	Wide excision	Removed	NR
Dale PS (1995) ⁷⁰	65	Silicone	7 years	13 cm	Wide excision	Removed	NR
Crestinu JM (1995) ⁷¹	NR	Silicone	2 years	NR	Wide excision	Replaced	NR
Aaron AD (1996) ⁷²	NR	Saline	2 years	NR	Wide excision & XRT (61 Gy)	Replaced	NR
Vandeweyer E (2000) ⁷³	45	Silicone	3 years	3 cm	Wide excision & XRT (45 Gy)	Removed	Recurrence-free at 2 years
Khanfir K (2003) ⁷⁴	52	Saline	1 year	8 cm	Methotrexate & vinblastine followed by hormonal therapy	Removed	Recurrence 8 months later; tumor resected
Jandali AR (2004) ⁷⁵	24	Silicone	9 years	6 cm	Wide excision	Replaced	Recurrence 3 years later; re-excision & XRT (50 Gy)
Gandolfo L (2006) ⁷⁶	22	Silicone	2 years	16 cm	Wide excision	Removed	NR
Jamshed S (2008)	30	Saline	3 years	5.6 cm	Wide excision	Removed	Recurrence-free at 2 years

NR=not reported; XRT=radiotherapy.

extent of a lesion at presentation and for surveillance following initial management. It is important to note that fibromatosis often extends microscopically beyond macroscopic margins.

The present literature describes 11 cases of fibromatosis related to breast prosthesis (Table 1).^{58,67-76} None of these patients had a history of FAP. In 5 cases the tumor arose from the capsule or was in continuity with it.^{58,67,71,73} Removal of the breast implant was necessary in all cases, and 4 patients had the prosthesis replaced.^{68,71,72,75} Three patients recurred at intervals of 7 months, 3 years, and unknown.^{58,74,75} All recurrences were treated successfully with additional local therapy.

The exact cause and effect relationship of fibromatosis to breast implants is unclear, but it may be related to a fibroblastic reaction to the surrounding capsule.

Conclusion

Fibromatosis is a locally aggressive, slow-growing tumor with a tendency to relapse but with no metastatic potential. Treatment should be individualized based on the location and extent of the lesion. Surgery is the mainstay of therapy, and the benefits of adjuvant radiotherapy and/or systemic therapy are questionable. Nonetheless, radiation therapy is an effective alternative for unresect-

able disease or poor surgical candidates. In addition, systemic treatment should be considered in cases of relapse and in those who are neither surgical nor radiation candidates; options include low-dose methotrexate and vinblastine, or hormonal therapy with or without an NSAID. Careful long-term follow-up is necessary at an institution with a multidisciplinary team specializing in treating sarcoma.

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Review

Aggressive Fibromatosis and Breast Implant

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The case presented by Jamshed and colleagues reports on an aggressive fibromatosis in a 30-year-old woman with a history of bilateral saline breast implant.¹ She had undergone surgical revision 3 months before a left anterior chest wall mass was noticed. A tumor originating from the left pectoralis minor muscle near the breast implant was identified. A biopsy established the diagnosis of fibromatosis. The patient subsequently underwent tumor resection with clear margins, with bilateral removal of the breast implants. The reconstruction of the chest wall and breast was performed.

Fibromatosis, also called desmoid tumor, is a rare disease and accounts for approximately 2–3% of all soft-tissue tumors.² Although histologically benign, it is a locally aggressive disease. It most commonly occurs in the musculature of the anterior abdominal wall.² Breast involvement is uncommon, and aggressive fibromatosis arising near breast prosthesis is exceedingly rare.³ This presentation has been the subject of 11 reports in the past. Of these 11 reported patients, 5 tumors grew near a saline breast implant and 6 near a silicone breast implant.³

Heredity, hormonal influence, trauma, Gardner syndrome, and previous surgical incision have been suggested as etiological factors of fibromatosis. Cytogenetic abnormalities consistent with clonality have also been reported.⁴

In the current case, the tumor appeared to arise from the fibrous capsule surrounding the implant. Although this may have played an etiologic role, a causal relationship is difficult to prove. It is possible that the implant or the surgical trauma, or both, acted as a trigger for the development of fibromatosis.

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Magnetic resonance imaging is helpful in diagnosis and may provide accurate information regarding size, location, and tumor extent.

Optimal management has not been clearly defined, as it can be based only on retrospective studies. For resectable tumors with expected good functional outcome, surgery with wide resection margins remains the primary treatment modality. Nevertheless, a high local recurrence rate is reported due to the infiltrative pattern of tumor growth.⁵

Possible treatment options include adjuvant or definitive radiotherapy and chemotherapy for unresectable primary or recurrent disease that is actively growing and has the potential for morbidity. Several retrospective studies support the use of radiation therapy and have suggested improved local control rates.^{6,7} In contrast, other studies found no advantage in local control using radiation therapy.⁸

Data from the literature suggest that gross residual disease may be controlled with radiation therapy alone using doses of 56 Gy, whereas irradiation doses of 50 Gy for microscopic disease appear to be adequate.^{6,7} The European Organization for Research and Treatment of Cancer has just completed a nonrandomized, phase II study of patients with inoperable or incompletely resected desmoid tumors treated with a radiation dose of 56 Gy delivered in 28 fractions of 2 Gy.

Some authors suggest systematic postoperative radiotherapy in patients with positive margins, whereas others recommend a policy of simple observation in these patients.^{7,8} This approach is based on reported cases of growth arrest or spontaneous regression of tumors.

Data on chemotherapy-treated fibromatosis are quite limited. Responses have been reported with drugs such as actinomycin D, or low-dose combinations of vinblastine/methotrexate- and doxorubicin-based chemotherapy.⁹

Other treatment options include antiestrogens,¹⁰ as well as nonsteroidal anti-inflammatory drugs, which have

been reported to confer a response rate of nearly 50%.¹¹ Other novel strategies include targeting platelet-derived growth factor receptor kinase,¹² but more data are needed to validate these results.

As was seen in this case and from the literature, we conclude that aggressive fibromatosis arising near a breast implant is very rare. Most data regarding this entity have come from studies of other tumor locations. When feasible, surgery is the mainstay of treatment for these patients. For unresectable or incompletely resectable tumors, a multimodality approach is indicated.

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