



## Case Report

# Desmoid-type Fibromatosis of the Breast. A Literature Review Based on 2 Case Reports

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## Abstract

The goal of this review is twofold; to highlight the difficulties in identifying, diagnosing, and treating desmoid-type fibromatosis (DF) of the breast and to discuss the current understanding of the key genetic mutations in the disease process that lead to specific treatment regimens. Currently, there are three groups of DF as classified by the World Health Organization (WHO): abdominal wall, extra-abdominal, and intrabdominal. They all present unique diagnostic challenges; however, the gold standard for diagnosis remains histopathologic confirmation even with the increased availability and sensitivity of imaging modalities. Given the importance of genetic alteration in this disease, the following three genes will be discussed: Catenin Beta 1, Rad51, and Poly Adenosine Diphosphate Ribose Polymerase-1. There is mounting evidence that these could potentially be targets for therapy in addition to surgery alone. Historically, diagnosis and treatment of DF of the breast have been difficult, which leads to a need for an interdisciplinary team approach composed of surgeons, pathologists, radiologists, oncologists, and internists which leads to the best overall care for patients with this pathology.

**Keywords:** desmoid fibromatosis; desmoid tumor; extra-abdominal desmoid tumor; aggressive fibromatosis, breast cancer

## Key Points

- Desmoid-type Fibromatosis is indistinguishable from malignancy on clinical presentation and imaging.
- The gold standard for diagnosis is biopsy with histologic evidence of beta-catenin staining.
- The etiology is currently unknown.
- Desmoid-type fibromatosis is locally aggressive and has a high risk of recurrence.
- Options for treatment include observation, hormonal therapy, chemotherapy, targeted therapy, radiation, and surgery.

## Introduction and Background

Desmoid-type fibromatosis (DF) of the breast, also known as extra-abdominal desmoid tumor, musculoaponeurotic fibromatosis, extra-abdominal desmoid aggressive fibromatosis, and low-grade sarcoma, is a rare benign tumor that creates a dilemma for multiple medical specialties such as internists, medical oncologists, surgeons, and radiologists [1]. DF of the breast is a rare benign tumor that should be included in the differential diagnosis for breast cancer particularly in patients that underwent surgery or had any kind of procedure of the breast tissue e.g. (implant placement or reconstructive surgery). DF is usually indistinguishable from malignancy on physical examination and imaging. The gold standard for diagnosis is made by histopathologic findings on biopsy of the tissue. This benign tumor has a specific pattern

of local aggressiveness, a small potential for metastasis, and a distinctiveness of having a high rate of postoperative recurrence. The optimal management of these types of tumors is composed of a multidisciplinary team with prior experience in soft tissue tumors because it can present in patients with a prior history of breast cancer who underwent surgery.

Fibromatoses are classified into three groups by the WHO. Fibromatosis of the abdominal wall (AF), extra-abdominal fibromatosis (EAF), and intraabdominal fibromatosis (IAF). IAF is often linked to familial adenomatous polyposis (FAP) while AF and EAF often occur sporadically. Desmoid-type fibromatosis is a locally aggressive, non-metastasizing, well-differentiated, and unencapsulated monoclonal myofibroblast proliferation with a tendency for recurrence and local invasion [2,3]. DF tumors have an aggressive tendency to infiltrate local structures causing mass effect, which can impair the function of adjacent organs or impede blood flow making some symptoms appear before the mass is evident [6].

## Case Presentations

### Case 1:

A 46-year-old female with a past medical history of hyperparathyroidism, asthma, past surgical history of cholecystectomy and oophorectomy for a benign cyst. Diagnosed with hormone receptor-negative extensive left breast ductal carcinoma in situ (DCIS) of the left upper outer quadrant for which she underwent a partial mastectomy. Sentinel lymph nodes were negative, and she completed radiation therapy after that. She underwent reduction mammoplasty bilaterally and a unilateral upper pole autologous augmentation with a biological mesh for reconstruction surgery. She underwent close follow-up with no new evidence of disease. Two years after the procedure, she developed a left lump for which she got a bilateral mammogram and ultrasound which showed a 34 mm hypoechoic mass in her left breast. Because of her history, she underwent an MRI, which showed a new progressive enhancement in the right medial chest with progressive kinetics, raising the question if she had breast cancer recurrence. A core biopsy of the lesion was done which showed skeletal muscle infiltrated by cytologically bland proliferation of fibroblastic/myofibroblastic cells arranged in fascicles in association with a variably prominent collagenous stroma. No evidence of malignancy was noted. While immunostaining for SMA was negative, multifocally striking positivity for beta-catenin was found. Beta-catenin exhibited nuclear immune reactivity. Pan keratin markers (AE1, AE 3, & PCK26) were negative, ruling out carcinoma and confirming extra-abdominal DF. Genetic testing was positive for a variant in the RAD51 gene, and BRCA1. BRCA 2 and other gene mutations were negative. A decision between the medical oncology team and the surgical team was made and

excision was recommended. The margins of excision were positive in the pectoralis major muscle, so she underwent subsequent surgery for exploration and re-excision of the chest tumor with full-thickness excision of the involved pectoralis major muscle. Subsequent biopsy showed no residual DF, and no further therapy was recommended.

### Case 2:

A 55-year-old female, with a past medical history of hypertension, bronchitis, kidney stones, thyroid nodule under observation, surgical history of abdominoplasty, bilateral breast reconstruction with expanders, and 2 cesarean sections. She had a history of stage IIa right breast DCIS that was hormone receptor-positive, HER 2 negative for which she received neoadjuvant chemotherapy with taxane, doxorubicin, cyclophosphamide, and radiotherapy. The patient underwent a subsequent bilateral nipple-sparing mastectomy, where 2/4 nodes were positive for lymphovascular invasion. Afterward, she underwent bilateral breast reconstruction with muscle-sparing latissimus dorsi myocutaneous flap and tissue expanders. The patient was followed up without any symptoms until 2 years later when she developed an enlarged right upper quadrant mass on the reconstructed breast for which a bilateral MRI was ordered. It showed a 61 mm enhancing mass in the left upper inner quadrant of the reconstructed breast pushing into the implant without invasion into the sternum or chest wall. An ultrasound-guided biopsy showed uniform proliferation of spindle cells with elongated vesicular nuclei that had eosinophilic cytoplasm. No significant cytological atypia or mitotic activity was noted. Immunostaining for CD 34, pankeratin, CK8-18, CK5/6, P63, keratin 903, and p63 was negative. Beta-catenin was the only positive marker, consistent with the diagnosis of fibromatosis. Treatment with excisional surgery with negative margins of 1 cm was performed with no adjuvant radiation or chemotherapy.

Although breast cancer recurrence must be ruled out when a patient has a recurrent breast mass, DF should be listed as a differential diagnosis; especially if the patient underwent any kind of surgery. DF falls in the middle of the category of fibrotic tissue reactions, which range from benign hypertrophic scars and/or keloids to the more severe malignant types like fibrosarcoma. The optimal management of DF is unknown as described. This has led to a lack of formalized guidance for practitioners managing this challenging condition that consequentially results in inconsistencies and the need for improvement in current management. The chances of surviving this tumor are excellent, however; the prognosis of recurrence is high [13]. Because there is evidence that desmoids form after various types of breast procedures (excisional biopsies, lumpectomies, mastectomies, breast reductions), their development may simply be the result of a cellular transformation in association with postsurgical scarring.

However, the possibility of such a transformation occurring because of the presence of foreign biomaterials is also a possibility that is a potential topic of further investigation. As the number of women electing to undergo breast augmentation increases and more cases are reported in the literature, an association between breast implants and DF may become more apparent [28]. A study by Ingley et al, used the Distress Assessment and Response Tool (DART) scores to estimate the prevalence and persistence of distress. It also compares cross-sectional data between DF and malignant sarcoma cohorts to identify predictors of distress. They found that adults with DF experience persistently high emotional distress compared to patients with malignant sarcoma. Women with abdominal wall DF and prior mood or current psychosocial concerns need early attention within multidisciplinary treatment settings to reduce persistent distress [29].

### **Epidemiology**

Cases of DF are often broadly categorized into one of two groups: Sporadic or FAP associated. Sporadic cases, which are the more common group, have an incidence of 3.42 per million persons years. This group represents 84 93% of all cases. Within this group, somatic  $\beta$  catenin-activating mutations are most of the drive mutations that cause the disease. The second group of cases consists of those associated with FAP. Regarding presentation, DF most commonly presents as a palpable painless firm breast mass [7]. The most common site for EAF is the shoulder and upper limb (33%) followed by the lower limb (30%), chest (18%), and head and neck (10%) [8]. Although DF typically occurs between the ages of 15 and 60 years. The peak incidence ranges from 25 to 35 years. The female-male ratio is 2:1 [6]. DF in general, has an annual incidence of approximately 2 to 5 cases per 1 million in USA and European populations and accounts for approximately 0.03% of all tumors. In the pediatric population, DFs are located primarily at extra-abdominal sites, affecting mainly bone, skeletal muscle, adjacent fascia, aponeurosis, and periosteum. In the adult population, they are frequently located intra-abdominally, affecting most commonly the gastrointestinal and genitourinary tracts [8]. The local recurrence rate after surgery with complete resection is 7–28% and 26–100% with incomplete resection. DF arising from the breast is very rare, accounting for 0.2% of all breast tumors [7]. Factors reported to increase the risk of recurrence include age (younger patients have an increased risk), involved margins, and site of origin (breast or pectoralis). The clinical presentation of DF is broad with initial presentation including an asymptomatic mass in young patients [5,9,10] following surgeries such as a latissimus dorsi myocutaneous pedicled flaps after breast surgery for recurrent breast carcinoma [11-13], or can present concomitantly with other types of tumors, for example, in case report showing its presentation after thyroidectomy for papillary thyroid cancer [14].

### **Pathophysiology**

There are many theories about the factors leading to the development of DF. Genetic mutations, like in the CTNNB1 gene, tissue trauma, hormonal factors, post-surgical reaction, and diseases like Gardner syndrome and FAP have been proposed as causes of DF [1,2,4,5]. The frequency of cases affecting young women during or after pregnancy, and the association with exposure to oral contraceptives supports the hypothesis of hormones aiding in the development of these tumors. Additional support for this theory is the noted regression in size in some patients during menopause [15]. In the study done by Fiore et al, 92 pregnant patients with DF showed that in 48% of cases, the onset of fibromatosis was related to pregnancy supporting the theory of hormonal influence [16]. Regarding genetic alterations, the most common ones described are CTNNB1, APC, Rad51, and PARP-1. (add a citation?)

### **CTNNB1**

Somatic mutations in the b-catenin (CTNNB1) gene located in chromosome 3p21 are believed to play a major role in the pathophysiology of sporadic DF tumor development [2]. This gene's most common single nucleotide polymorphisms (SNPs) are T41A, S45F, and S45P [3]. A case report of a 5-year-old patient with DF was also found to be positive for an A-to-G transition at codon 41 of the CTNNB1 gene [17]. The diagnosis can further be confirmed by screening for mutations (mainly in exon 3) of the  $\beta$ -catenin gene, which is found in 85% of sporadic cases [8]. The pathological mechanism proposed for tumor development with this mutation is increased activity of the WNT signaling pathway leading to uncontrolled proliferation. This increased expression can be explained by a mutation of the B-catenin gene, or less frequently, of the 3' region of the adenomatous polyposis coli (APC) gene. The APC variant is more prevalent in the intra-abdominal fibromatoses associated with Gardner's syndrome. These mutations lead to an accumulation of intracytoplasmic and intranuclear B-catenin, which can be validated immunohistochemically and serves as the gold standard for diagnosis [6]. The protein APC, which regulates cellular  $\beta$ -catenin, is involved in wound healing and fibroproliferation. The consequence of this mutation is a translocation of cytoplasmic  $\beta$ -catenin into the nucleus that activates the expression of T-cell factor, and this upregulates the expression of downstream genes such as cytochrome c oxidase 2 (COX-2), platelet-derived growth factor (PDGF) and retinoblastoma 1 (RB1) [8]. COX-2 promotes tumor growth via inhibition of apoptosis, stimulation of angiogenesis, migration, and cell proliferation by increasing the expression of growth factors [16]. This high expression of COX-2 is the reason behind some NSAIDs being given as treatment for this disease, which will be further discussed.

A meta-analysis of patient data by Kadowaki et al. assessed the association between recurrence and CTNNB1 mutation status in surgically treated patients with DF [3]. Out of 329 patients, 46.8% had a T41A mutation, 20.1% a S45F mutation, and 7.3% a S45P mutation. Overall, 25.2% of the patients in the study experienced recurrence. Out of all the mutations, the sporadic DTFs harboring an S45F mutation had a higher risk of recurrence after surgery compared to T41A and S45P but this association seemed to be mediated by tumor size [3]. DF is not the only type of tumor that has been related to CTNNB1 mutations. Desmoplastic fibroma of bone (DFB) is an osseous counterpart of DF that also exhibits CTNNB1 mutations.

### Rad51

Rad51, a gene found on chromosome 15q15.1, belongs to the system of DNA repair genes. RAD51 protein encoded by its gene has a significant effect on repairing damaged DNA and maintaining genomic integrity. 135 G/C and 172 G/T are two common RAD51 single nucleotide polymorphisms (SNPs), which might influence mRNA stability and lead to carcinogenesis [18]. This mutation can promote cancer progression by two distinct mechanisms: indirectly via altered homologous recombination (HR) and directly by upregulating pro-metastatic gene expression. The presence of this mutation has been previously reported in cancers such as head and neck, esophageal, and Polish men with prostate cancer. It has even been proposed as a marker to measure for patients with breast cancer who are resistant to aromatase inhibitor therapy [18-20]. A study by Nowacka-Zawisza et al. concluded that patients with metastatic prostate cancer who did not respond to standard treatment should be evaluated for this mutation [19]. In cancers such as cervical cancer, this gene has been reported to influence cell radiotherapy resistance. A study indicated that miR-4429 promoted cervical cancer cell radio-sensitivity by targeting RAD51, providing a potential therapeutic target for cervical cancer patients [22]. A successful invitro study, reported that the use of cisplatin and Nutlin-3 could potentially inhibit RAD51 [23]. However, currently only one clinical trial is ongoing that targets RAD51 [21]. The early results of these studies could encourage more RAD51 research resulting in a potentially clinically significant targetable mutation.

### PARP-1

Poly Adenosine Diphosphate Ribose Polymerase-1 (PARP-1) is a DNA-repairing enzyme. It may be a pathogenetic factor, and it could become a target for therapy as shown by the successful treatment of selected carcinomas and sarcomas by PARP-inhibitors. In a study by Bräutigam et al., they assessed the expression of estrogen receptors (ER), progesterone receptor (PR), androgen receptor (AR), as well as PARP-1 via immunohistochemistry and quantitative RT-PCR in 69 tissue samples of desmoid

tumors. Overall expression patterns were correlated with clinical-pathologic parameters to determine their value as a prognostic factor. According to this study, PARP-1 expression is associated with a poorer prognosis that is, in part, due to faster recurrence. This highlights the possibility of PARP-1 inhibitors as a targetable option in DF. Currently, PARP inhibitors are used in specific types of cancers such as breast, ovarian, pancreatic, and metastatic castration-resistant prostate cancer and potentially DF. Of note, hormone receptors were of minor prognostic relevance in this study showing a significant difference with other types of tumors such as breast cancer [24].

### Histology

The gold standard for diagnosis of DF is histopathologic confirmation. Cytologic examination by fine needle aspiration (FNA) is usually not diagnostic, so a core needle biopsy or total excision is preferred. Definitive preoperative pathological diagnosis by either FNA or core needle biopsy is difficult as the histological findings can be nonspecific, and biopsies are often interpreted as showing only benign fibrosis or inconclusive findings [25]. Image-guided core needle biopsy is an accurate, safe, and relatively cost-effective method of diagnosing DF [6]. Desmoid tumors consist of well-differentiated myofibroblastic cells set in a variably collagenous matrix [6]. The neoplastic cells expand into the adjacent tissues. Low to moderate cellularity, arranged in fascicles of spindle cells in a uniform direction is seen. Elongated blood vessels are frequently observed running parallel to the fiber direction. The spindle cells have a myofibroblastic appearance; with a low nuclear to cytoplasmic ratio [2]. Lymphocytic infiltrates are sometimes present at the periphery of the lesion. This contrasts with inflammatory lesions that generally demonstrate inflammatory cells throughout the tissue [4]. The lesion does not have malignant features such as a high mitotic rate, cellular atypia, necrosis, or vascular invasion. Immunohistochemical staining for  $\beta$  catenin with nuclear positivity is the most useful tool in establishing a diagnosis [7]. Nuclear staining for  $\beta$ -catenin is a consistent finding in more than 80% of cases [8]. Immunohistochemistry findings for intra-abdominal DF are positive for vimentin and  $\beta$ -catenin and negative for Smooth Muscle Actin (SMA) such as S100, CD117, and CD34.

Other lesions in the differential diagnosis, which should be excluded, include solitary fibrous tumor (STAT6 positive), glomangiopericytoma (peritheliomatous hyalinization, patternless proliferation, extravasated erythrocytes, and inflammatory cells), perineurioma (EMA, claudin-1, GLUT1 positive), ossifying fibroma, hypertrophic scars, and chondromyxoid fibroma [2].

### Imaging

DF gross appearance significantly varies in appearance and size. Most lesions are lobulated, firm, poorly defined, and grayish

[4,5,12]. Generally for DF, MRI with and without contrast is the preferred imaging technique for assessment of the tumor size, invasion extension, and for future surgical procedure planning. DF of the breast is characterized as an irregular mass that mimics cancer on various modalities of imaging including mammogram, breast ultrasound, and MRI. Appearance on mammography is typically a spiculated high-density mass and rarely presents calcifications. An irregularly shaped hypoechoic mass is the most common imaging result on ultrasound. It is important to note that not all desmoid tumors are visible by mammography or ultrasound. A series by Neuman et al. showed that the tumor was visible mammographically only in a third of patients [25]. On MRI imaging, desmoid tumors have been described as isointense masses on T1-weighted images, and as lower or higher-intensity lesions on T2-weighted images. With contrast enhancement, a heterogeneous enhancement atypical of breast carcinoma is typically described [25].

## Treatment

The management of DF is based on the experiences derived from previous uncontrolled studies [15]. A standardized treatment for DF of the breast has not been established because of the low prevalence of the disease. Options include a broad list of pharmacological options such as nonsteroidal anti-inflammatory drugs (NSAIDs), hormonal agents such as Tamoxifen, chemotherapy, tyrosine kinase inhibitors, radiation, cryoablation, surgery, or observation without any kind of procedure with follow-up imaging, preferably MRI. It has previously been accepted that wide local excision should form the cornerstone of DF management. More recently a paradigm shift in management has resulted in many clinicians adopting a more conservative approach. Emphasizing preservation of anatomical structures, avoidance of mutilating surgery, and the use of adjuvant therapy. This change in mindset followed the acknowledgment that desmoid tumors follow a variable and unpredictable natural history. In addition, a significant proportion of cases either do not progress or undergo spontaneous regression. Recognition that non-surgical therapies have a more central role to play in the management of DF also contributed to this shift in management [6].

In general, DF should be treated by a multidisciplinary group consisting of internists, medical oncologists with experience in soft tissue tumors, radiologists, interventional radiologists, and oncologic and plastic surgeons. Before 2000, most breast DF were surgically removed, but radical surgery was frequently unsuccessful due to incomplete resections and high rates of recurrence. A better understanding of the biology of these tumors and the introduction of new medications has enabled the development of medical protocols using targeted therapies. If re-excision would result in significant cosmetic or functional deformity, the option of close observation is preferred. Local recurrences usually occur within 3

years of the initial diagnosis. During this period, close follow-up is suggested with imaging done preferentially every 3-6 months [4].

A case report of a patient managed with medications showed a good response. This case was of a female patient with DF of the breast that received NSAIDs, tamoxifen, and triptorelin (GnRH agonist that reduces the risk of ovarian cysts seen with tamoxifen). This was followed by Sorafenib, interferon  $\alpha 2b$ , and finally Sunitinib. Because the patient was planning a pregnancy at some point and her young age; removal by surgery, cryotherapy, or radiotherapy was deferred by the patient and subsequently TKIs were pursued [16]. The exclusive medical treatment that this patient underwent allowed for a reduction of more than half of the tumor volume [16].

A systematic review evaluated the efficacy of low-dose chemotherapy with methotrexate and vinblastine as a treatment modality for extra abdominal desmoid-type fibromatosis. They describe a response rate (complete remission (CR) or partial response (PR)) of 36%. Clinical benefit was consistently as high as 85%. The mean adverse event rate was 31%. The most common adverse event was neutropenia. The authors concluded that the efficacy of this chemotherapy was convincing, however; they only weakly recommend this chemotherapy regimen [26]. Meazza et al reported a 22% versus 76% recurrence rate of DF when negative versus positive surgical margins were compared. This has led to the use of adjuvant chemotherapy when positive margins are reported, or recurrences occur [11].

Selective estrogen receptor modulators (SERMs) are compounds with a mixed agonist/antagonist activity on estrogen receptors. Recently, raloxifene, a second-generation SERM, has been used in the treatment of FAP patients affected by DF. The mechanisms through which these molecules affect desmoid tumor growth appear to be, in part, because SERMs may act independently of estrogen receptors [15]. All the studies published with SERMs, either tamoxifen or raloxifene, in patients affected by desmoid tumor suffer an important limitation; the lack of a multi-center, randomized, controlled clinical trial, as with the other treatment modalities here described [15].

Penel et al. el conducted a nationwide prospective cohort study from a French Sarcoma group where they evaluated surgical versus non-surgical approaches in primary DF. 771 confirmed cases of DF were analyzed. Overall, the 2-year event-free survival (EFS) was 56%. This value did not differ between patients undergoing surgery and those managed by observation. The 2-year EFS was 66% for favorable locations (abdominal wall, intra-abdominal, breast, digestive viscera, and lower limb) and 41% for unfavorable locations such as with lymphovascular invasion. Among patients with favorable locations, the 2-year EFS was similar in patients treated by both surgery and the observational

approach. Among patients with unfavorable locations, the 2-year EFS was significantly enhanced in patients initially managed with the observation approach (52%) compared with those who underwent initial surgery (25%) [27]. Observational approach was defined as follow-up imaging at 3, 6, and 12 months.

The National Comprehensive Cancer Network (NCCN) suggests an approach to these tumors with a multidisciplinary team with experience in soft tissue tumors. They also recommend evaluation for Gardner syndrome and FAP. They recommend CT or MRI with contrast as appropriate unless contraindicated. After biopsy and diagnosis are made, they split the treatment modalities into resectable or non-resectable. If the tumor is classified as resectable, they suggest either medical/surgical intervention or observation. If treatment is chosen, surgery or radiotherapy with or without systemic therapy can be done. Systemic therapy options include sulindac or celecoxib, tamoxifen with or without sulindac, toremifene, methotrexate with vinblastine, low-dose interferon, doxorubicin-based regime, imatinib, sorafenib, MTX with vinorelbine, or liposomal doxorubicin. Bonvalot et al. published their treatment algorithm consisting primarily of serial MRI and an observation approach. Only if progression occurred was medical therapy instigated with a SERM and chemotherapy. If further significant progression occurs then surgery, isolated limb perfusion, and/or radiotherapy is suggested. Of five case reports that were managed with observation only one underwent significant radiologic progression [6].

Neuman et al looked prospectively at a sarcoma database at Memorial Sloan-Kettering Cancer Center for desmoid tumors involving the breast treated at that institution between 1982 and 2006. Thirty-two patients were identified, but only twenty-eight patients had adequate follow-up. The majority (94%) of patients were female with a median age at diagnosis of 45 years. Two patients (6%) had a diagnosis of FAP and a prior history of desmoid tumors. One patient was being treated with tamoxifen for an intraabdominal desmoid tumor when the desmoid tumor of the breast developed. Eight patients (25%) had a history of ipsilateral breast cancer, and one patient (3%) had a history of an ipsilateral phyllodes tumor [25]. Prior breast surgery had been performed in 14 of 32 patients (44%). This included breast reduction mammoplasty in two patients (6%), breast augmentation in two patients (6%), excisional biopsy in two patients (6%), wide excision in one patient (3%), and mastectomy in seven patients (22%). Of the seven patients who had undergone mastectomy, four had an axillary node dissection and five subsequently underwent breast reconstruction (two with tissue and three with implants). Patients presented with desmoid tumors within a median of 24 months following their previous procedure. All 32 patients presented with physical findings suspicious of carcinoma. Twenty-eight (87.5%) had a palpable mass at presentation and six (18.75%)

had skin retraction or dimpling. Two additional cases presented with capsular contracture after breast implants. In patients with a history of modified radical mastectomy, the presenting mass occurred throughout the dissection field. These sites included the axilla, the costal margin, and in the reconstructed breast. Radiologic findings for a mass suspicious of carcinoma were visualized in six patients (38%) but were undetected in 10 of 16 patients (62%). Eight of those ten patients had a palpable mass. All nine patients (100%) who underwent breast ultrasound were found to have a solid hypoechoic mass. Eight patients underwent preoperative magnetic resonance imaging (MRI) of the breast. In all eight cases, MRI visualized a mass. MRI enhancement patterns varied among the patients where the masses were considered suspicious for carcinoma in most of the patients. In three patients, an MRI was performed after a negative mammogram. Two patients had a prior history of ductal carcinoma in situ and an MRI was performed as part of the workup for presumed cancer recurrence. Treatment of the desmoid tumor was primarily surgical. In 78% of cases, an incisional or excisional biopsy was performed as the initial surgical procedure to obtain a pathological diagnosis. Of the thirty patients, five had estrogen and progesterone receptor testing performed on the specimen. All five of which were negative. One patient was treated with 6 weeks of celecoxib before surgical resection with a partial clinical response. One patient early in the series was treated with implanted iridium-192 seeds after a large chest wall resection with positive margins. 29% of the patients developed a tumor recurrence. Recurrence after treatment for the desmoid tumors occurred at a median of 15 months. In 90% of the patients, recurrence happens within 3 years. Recurrences were managed with surgical resection in 80% of the patients. Three patients received radiation in addition to the surgical resection. One patient with a biopsy-confirmed recurrence was treated with tamoxifen alone with a complete clinical response (estrogen and progesterone receptor status was not reported). One patient did not receive treatment because of comorbidities. Two patients experienced multiple recurrences [25]. Clinical and pathological factors predictive of recurrence were evaluated which showed that younger patients experienced more recurrences. The average median patient age that had recurrence was 28 years compared to a median of 46 years in those who did not have recurrence. No differences in recurrence rates in patients with and without a history of prior surgery were observed. Of the 8 patients who developed a tumor recurrence, 5 out of the total 9 (63%) patients had positive margins at the time of the initial resection. In comparison, 3 of 19 patients (16%) with negative margins developed a tumor recurrence. They report that surgical trauma before the development of a desmoid was present in 44% of the patients. Several published cases have reported desmoid development after the placement of breast implants (either saline or silicone). In these case series, five of the thirty-two described were males [25].

DF arising near a breast prosthesis is a rare event. Such cases have indeed been documented after surgical placement of breast implants. This led to the hypothesis that these tumors may arise from the fibrous capsule developing around the implant [1].

## Conclusion and Discussion

Desmoid tumor of the breast is an extremely rare entity and should be considered in the differential diagnosis of recurrent breast mass or post-operative changes. The diagnosis of DF is usually incidental and challenging. Pathological and immunohistochemical testing are essential for confirming diagnosis. Demonstration of  $\beta$ -catenin nuclear staining is the single most important characteristic [8]. Most patients present with a palpable breast mass that is suspicious for malignancy both clinically and radiographically. The optimal treatment of DF remains controversial. A general shift to a more conservative observational management strategy has recently taken place with no apparent detrimental effects on oncologic outcomes. All patients in whom a diagnosis of DF is considered should be imaged appropriately, ideally MRI, undergo a planned biopsy, via radiologically guided core needle biopsy, and be managed by a sarcoma multidisciplinary team [6]. Therapy for desmoid tumors of the breast remains surgical and no strong predictors of recurrence exist. Given the conflicting data in the literature on the association of margin status and recurrence, it seems prudent to strive for negative margins during surgical resection. However, when destructive procedures such as extensive chest wall resections are necessary to achieve a complete resection; observation or a trial of radiation or adjuvant therapy is reasonable [25]. Tumor size and CTNNB1 mutation type should be considered as predictors for recurrence in patients with extra-abdominal surgically treated primary sporadic DF. Mutation type should be included in the management algorithm for managing DF [3]. Medical treatments available to date have heterogeneous efficacy. Targeted therapies may be a serious option to consider especially when surgery is considered high risk. We hope that with our case reports and review, additional research will be performed that will enhance our understanding and management of this rare disease.

**Conflict of Interest:** The authors declare no conflict of interest that could have affected the preparation of this manuscript.

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