Biology and Treatment of Aggressive Fibromatosis or Desmoid Tumor

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Abstract

Aggressive fibromatosis, also known as desmoid-type fibromatosis (DTF) or desmoid tumor, is an uncommon locally invasive tumor. Because of its low incidence and variable behavior, DTF is often first seen by physicians who are not familiar with it, and recent advances in understanding this disease have led to changes in treatment approaches. The Wnt (β-catenin) pathway appears to play a key role in DTF pathogenesis, and recent studies of DTF biology suggest a possible model of DTF pathogenesis. Histologically, DTF shows a poorly circumscribed proliferation of myofibroblast-like cells with variable collagen deposition, similar to the proliferative phase of wound healing, and DTF has been associated with trauma and pregnancy. Desmoid-type fibromatosis may be a useful model of the tumor stroma in carcinomas as well as other fibrosing diseases such as progressive pulmonary fibrosis. The clinical course of DTF can vary greatly among patients, complicating the determination of the optimal treatment approach. Treatment options include surgery, nonsteroidal anti-inflammatory drugs with or without hormonal manipulation, chemotherapy, radiation therapy, and other forms of local therapy. Many treatments have been used, but these are not without toxicities. Because of the variable nature of the disease and the potential morbidity of treatment, some cases of DTF may do better without treatment; simple observation is often the best initial treatment. This review used a PubMed search from January 1, 1980, through October 31, 2016, using the terms fibromatosis and desmoid and discusses DTF disease characteristics, pathophysiology, and treatment options as well as examines several cases illustrating key points in the biology and treatment of this heterogeneous disease.

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The term fibromatosis encompasses 2 general groups of tumors: superficial and deep fibromatoses. The superficial fibromatoses include palmar fibromatosis or Dupuytren contracture, plantar fibromatosis, and penile fibromatosis or Peyronie disease. Deep or aggressive fibromatosis, also known as desmoid-type fibromatosis (DTF) or desmoid tumor, is a clonal locally invasive tumor that does not metastasize. However, although uncommon, DTF may be multifocal. The word desmoid derives from the Greek desmos meaning “bandlike, bond, or fastening.” Desmoid-type fibromatosis was originally described by McFarlane in 1832 and termed “desmoid tumor” by Mueller in 1838. By 1904, about 400 cases had been reported. The term fibromatosis was later introduced by Stout. This review used a PubMed search from January 1, 1980, through October 31, 2016, using the terms fibromatosis and desmoid.

Histologically, DTF shows a poorly circumscribed proliferation of myofibroblast-like cells with variable collagen deposition. These myofibroblastic cells are histologically similar to the proliferative phase of wound healing, and DTF has been associated with trauma, pregnancy, and oral contraceptive use. Trauma is a common inciting agent for the development of DTF, and surgery may sometimes promote growth of DTF. The natural history of DTF is highly variable. This review discusses DTF disease characteristics, pathophysiology, and treatment options as well as examines several cases illustrating key points in the biology and treatment of this heterogeneous disease.

EPIDEMIOLOGY OF DTF

Desmoid-type fibromatosis most commonly arises between the ages of 15 and 60 years, with a female predominance of 2- to 3-fold. The incidence of DTF is about 2
In contrast, the incidence of DTF is lower; in some studies, the incidence of DTF is estimated to be 4 per million per year in the general population. In contrast, the incidence of DTF has been reported to be about 1000-fold higher in patients with familial adenomatous polyposis (FAP), in which the adenomatous polyposis coli gene (APC) is mutated. Familial adenomatous polyposis—associated DTF is more frequently abdominal, especially in the Gardner variant of FAP, which is characterized by intestinal polyposis, osteomas, fibromas, and epidermal inclusion (“sebaceous”) cysts. Desmoid-type fibromatosis develops in approximately 5% to 30% of patients with FAP, usually in the mesentery. In some studies, FAP-associated DTF represents about 2% of DTF cases; in 1 Dutch study, nearly 10% of patients with DTF have or will develop FAP. With aggressive follow-up of patients with FAP and in those receiving prophylactic colectomy, DTF has been reported to be the most common cause of death. Kindreds of familial DTF without the colonic features of FAP have also been reported in which mutations occur in a different region of APC. Genetic predisposition to DTF in patients with FAP independent of germ line APC mutation has also been described, suggesting the existence of genes independent of APC that influence DTF formation in FAP. Although common in patients with FAP, most cases occur sporadically in young adults and are associated with a mutation in β-catenin (CTNNB1). Desmoid-type fibromatosis and a related disease, infantile aggressive fibromatosis, may also differ between children and adults. Infantile fibromatosis (so-called diffuse or mesenchymal type of fibromatosis) is not discussed here and usually occurs before the age of 2, most commonly in the first few months of life; it may recur locally, but does not metastasize.

**HISTOLOGY OF DTF**

Histologically, DTF appears as a poorly circumscibed proliferation of myofibroblastic cells with variable collagen deposition. Typically, the margins of the tumor are difficult to assess at the time of surgery, and the final margins are often positive. Desmoid-type fibromatosis tumors are morphologically heterogeneous and may exhibit striking morphological intra- and intertumoral heterogeneity. In some areas tumors may resemble fibroblasts of inactive fibrous tissue, whereas other areas resemble the active fibroblasts of wound healing. This morphological heterogeneity covers a spectrum ranging from areas in which cells have oval nuclei containing pale-staining vesicular euchromatin and small nucleoli to areas in which cells have elongated nuclei that stain darkly with hematoxylin, reflecting heterochromatin. Cells with more euchromatin are presumably more “transcriptionally active,” whereas cells with more heterochromatin are felt to be more “transcriptionally inactive.” Figure 1, B, shows an area that appears inactive, with sparse cells with narrow, darker-staining nuclei and few mitoses, in which in general there is more collagen deposition, imparting a more pink (collagenous) coloration to these inactive areas. Typically the areas with more “transcriptionally inactive” cells are often separated by extensive collagen.

**ARTICLE HIGHLIGHTS**

- The clinical course of desmoid-type fibromatosis (DTF), an uncommon locally invasive tumor, can vary greatly among patients, complicating the determination of the optimal treatment approach.
- The Wnt (β-catenin) pathway appears to play a key role in DTF pathogenesis.
- Treatment options include surgery, nonsteroidal anti-inflammatory drugs with or without hormonal manipulation, chemotherapy, radiation therapy, and other forms of local therapy. Many treatments have been used, but these are not without toxicities.
- Because of the variable nature of the disease and the potential morbidity of treatment, some cases of DTF may do better without treatment; simple observation is often the best initial treatment.
- Desmoid-type fibromatosis may be a useful model of the tumor stroma in carcinomas as well as other fibrosing diseases such as progressive pulmonary fibrosis.
greater cell density, increased mitotic activity, and less collagen. Digital assessment of chromatin density and average nuclear size and pathological assessment of tumor activity were strongly correlated in 1 study, and there was a spatial correlation of protein expression of genes overexpressed in DTF and nuclear morphology.

**GENETIC CHANGES IN DTF**

The Wnt (β-catenin) pathway appears to play a key role in DTF pathogenesis, with a mutation in the β-catenin gene in most sporadic cases, or a mutation in APC, which regulates β-catenin degradation, in cases associated with FAP.

In 1 study a
CTNNB1 mutation was found in 223 of 254 sporadic DTF cases (88%), with only 3 mutations reported: S45P, S45F, and T41A. S45P and T41A were the most common, with S45P seen in less than 10% of cases. Several cases of APC mutations have also been found in sporadic cases of DTF. Clonal chromosomal changes have been reported in about 45% of cases of deep DTF and approximately 10% of superficial fibromatosis cases, with several recurrent chromosomal changes reported. In a study of 17 FAP-associated DTF and 38 sporadic DTF cases using comparative genomic hybridization and multiple ligation-dependent probe amplification, a limited number of genetic changes was observed in 44% of tumors. A higher frequency of copy number abnormalities was seen in FAP-associated DTF (59%) as compared with sporadic DTF (37%). The incidence and severity of DTF in FAP is related to the site of APC mutation.

MOLECULAR BIOLOGY OF DTF

Desmoid-type fibromatosis exhibits a monoclonal proliferation of myofibroblasts, presenting a true neoplastic process and as described above, the Wnt or ß-catenin pathway has been strongly implicated in DTF pathogenesis. In addition, induction of stabilized ß-catenin in a transgenic mouse model leads to hyperplastic cutaneous wounds and the development of DTF, providing further evidence that ß-catenin plays a role in these fibroproliferative diseases. Similarly, mice with germ line mutations in APC have a high incidence of DTF. Abnormal growth factor production (including transforming growth factor [TGF] and platelet-derived growth factor [PDGF]) has been associated with hereditary gingival fibromatosis and plantar fibromatosis and may play a role in DTF as well. Murine studies suggest that DTF can originate in mesenchymal stem cells, in some cases derived from pericytes.

ß-Catenin, encoded by the CTNNB1 gene, is also mutated or overexpressed in various cancers and has 2 recognized functions. It is part of the cadherin complex involved in cell-cell adhesion, in which it binds the cytoplasmic domain of cadherin, and also, as part of the Wnt signaling pathway, can translocate to the nucleus in which it regulates gene transcription. ß-Catenin is regulated by a destruction complex including APC, which has multiple ß-catenin binding sites, axin, casein kinase 1 (CK1), glycogen synthase kinase 3ß (GSK3), and protein phosphatase 2A. ß-Catenin is phosphorylated in this complex by GSK3 after a “priming” phosphorylation by CK1, which leads to ubiquitination and subsequent degradation in the proteasome. Wnt signaling from the cell surface leads to disruption of the APC/axin/GSK3 complex and thus inhibits ß-catenin phosphorylation by the complex, leading to increased nuclear ß-catenin.

Nuclear ß-catenin can act as a transcriptional activator when bound to a member of the T-cell factor/lymphocyte enhancer family, leading to the formation of nuclear ß-catenin/T-cell factor/lymphocyte enhancer complexes, changing the way they bind promotor regions of DNA and altering gene transcription. The hedgehog signaling pathway and ß-catenin signaling pathways regulate each other’s activity, and 1 study found that hedgehog signaling is activated in human and murine desmoid tumors.

Four genes—a disintegrin and metalloproteinase gene 12 (ADAM12), fibroblast activation protein 1α (Fap-1α), Wnt 1 inducible signaling pathway protein-1 (WISP1), and SRY-box 11 (SOX11)—have been reported to be overexpressed in DTF compared with 16 nonneoplastic tissues, and immunohistochemistry studies have exhibited protein expression of ADAM12, Fap-1α, WISP1, and SOX11 in DTF. Fap-1α is a serine protease localized to the cell surface and cytoplasm. Fap-1α has been found in tumor stroma and several fibrotic diseases including idiopathic pulmonary fibrosis. ADAM12 plays a role in cell-cell and cell-matrix interactions and regulates integrin signaling; ADAM12 expression has also been found in Dupuytren disease and idiopathic pulmonary fibrosis (reviewed in reference 80). ADAM12 identifies a proinflammatory subset of PDGF receptor-α (PDGFR-α)—positive stromal cells residing in the perivascular space that can be activated by acute injury and can differentiate into myofibroblasts and act as progenitors for a large fraction of the collagen-producing cells generated in scarring; these cells are progressively...
eliminated during normal wound healing.\textsuperscript{80} WISP1 is a secreted protein that can act as a growth factor and regulate various cellular functions.\textsuperscript{81} WISP1 has been detected in a number of tumors, including the desmoplastic tumor stroma of carcinomas\textsuperscript{82} and DTF.\textsuperscript{48,51,83,84} WISP1 is up-regulated in idiopathic pulmonary fibrosis and stimulates extracellular matrix (ECM) deposition by fibroblasts.\textsuperscript{85} SOX11 is a nuclear transcription factor that is temporally regulated in development and not expressed in most adult tissues. SOX11 is deregulated in various tumors\textsuperscript{86} and overexpressed in liposarcomas.\textsuperscript{87} SOX11 is more highly expressed in mesenchymal stem cell lines than in fibroblasts and may aid mesenchymal stem cell proliferation and pluripotent potential retention.\textsuperscript{88}

Thus, the available data suggest a possible model of DTF pathogenesis, in which an activating stimulus, such as trauma with associated inflammation and growth factor production, in the setting of deregulation of $\beta$-catenin, leads to up-regulation of $\beta$-catenin\textsuperscript{48} (Figure 3, right side). Reactive oxygen species produced by neutrophils have been shown to have the potential to induce mutations in DNA. In rare cases the inciting event may stimulate a progenitor cell that does not have baseline $\beta$-catenin dysregulation.
β-Catenin can then translocate to the nucleus, complex to transcription factors, bind the WISP1 promotor, and increase WISP1 production. WISP1 may then bind its receptor and induce β-catenin nuclear translocation, resulting in a prosurvival signal, and further stimulate WISP1 production and production of extracellular matrix (ECM) proteins including collagen, leading to fibrosis. WISP1 binding to the tumor cells can also further stimulate tumor growth. WISP1, by binding to its receptor on other cells, may also recruit nonclonal (normal) profibrotic ADAM12-positive cells from a PDGFR-α-positive precursor pool, potentially adding nonclonal normal myofibroblasts to the tumor. These recruited cells, whether normal or part of the true clonal tumor, are Fap-1 positive and produce a number of ECM proteins, leading to fibrosis. In rare cases, an inciting stimulus may activate cells that lack β-catenin dysregulation (left-hand-side of the figure). The exact role of ADAM12 and Fap-1 is unknown, but may modify signaling via protease activity. Although the role of SOX11 is also not clear, studies have reported that SOX11 assists mesenchymal stem cell proliferation and retention of pluripotent potential.

(left-hand-side of the figure). β-Catenin can then translocate to the nucleus, complex to transcription factors, bind the WISP1 promotor, and increase WISP1 production. WISP1 may then bind its receptor and induce β-catenin nuclear translocation, resulting in a prosurvival signal, and further stimulate WISP1 production and production of ECM proteins including collagen, leading to fibrosis. WISP1 binding to the tumor cells can then further stimulate tumor growth. Myofibroblasts are functionally heterogeneous and can be generated from multiple cell types. WISP1, by binding to its receptor on other cells, may also recruit nonclonal (normal) profibrotic ADAM12-positive cells from a PDGFR-α-positive precursor pool, potentially adding nonclonal normal myofibroblasts to the tumor. These recruited cells, whether normal or part of the true clonal tumor, are Fap-1 positive and produce a number of ECM proteins, including collagen, leading to fibrosis. In some cases DTF tumors, and their constituent cells, may stabilize or regress, with a decrease in expression of ADAM12, FAP-1α, WISP1, and SOX11 (Figure 4). In most cases of DTF, different areas of the tumor show either active or inactive areas, indicating that the balance of these factors leading to progression or regression operate differently in different parts of the tumor. The mechanisms regulating these factors are unknown.
EVIDENCE FOR CLINICAL TREATMENTS OF DTF

The natural clinical course of DTF can vary greatly among patients, complicating the determination of the optimal treatment approach. Clinical trials exhibiting the best approach in a particular patient are lacking. Treatment options include surgery, nonsteroidal anti-inflammatory drugs with or without hormonal manipulation, chemotherapy, radiation therapy, and other forms of local therapy. Many treatments have been used, but these are not without toxicities. Because of the variable course of the disease and the potential morbidity of treatment with the result that some cases of DTF may do better without treatment, Lewis et al.90 Mitchell et al.91 and Rock et al92 were among the first to suggest that simple observation may often be the best initial approach, and this recommendation has become more common.93-103 Some studies suggest that approximately 50% of cases will have an indolent course95 and that patients with DTF who have stable disease for more than 1 year are unlikely to require active treatment.96,104 The therapeutic approach of adults with DTF and children with either DTF or infantile aggressive fibromatosis may also differ.45,46

Abdominal wall desmoids are most commonly associated with pregnancy and could relate to “trauma” of stretching the abdominal wall musculature or possibly hormonal changes or both.14 However, pregnancy is also associated with changes in circulating growth factors and immune modulators, including vascular endothelial growth factor, TGF-β, and insulin-like growth factor 1; these all could also be involved.105-108 Spontaneous regression of cases of abdominal wall DTF occurred in about 30% of patients in 1 series of 122 patients not treated with surgery for DTF.96 In another study of 147 patients, 97% of whom were young women with abdominal wall DTF, 102 underwent initial observation; of these, 29 had spontaneous regression and only 16% went to surgery by 3 years.95 Although the rate of progression of DTF diagnosed during pregnancy is high, its prognosis is generally good,109 and is not necessarily, a contraindication for further pregnancies.110 Trauma, as from surgery, may worsen DTF, and DTF has a high risk of local recurrence after surgery ranging from about 25% to 60% at 5 years.19,31,59,94,111-120 Inflammation from other types of trauma also may augment or stimulate recurrence; however, DTF does not metastasize. Although a marginal resection is associated with a worse outcome than a complete resection, the nature of the surgical procedure is strongly influenced by tumor location and associated anatomical and functional consequences.99 In a retrospective study of a subgroup of patients, the 3-year event-free survival with a nonsurgical approach was similar to that after a complete resection.94 A multivariate analysis of 495 patients undergoing gross resection found that only age, tumor size, and tumor location site were associated with recurrence, with younger age having a worse prognosis.121 In another multivariate analysis of 426 cases of sporadic DTF, 87% of cases were treated surgically, and about 50% of cases recurred; only age, tumor size, and tumor site were independent prognostic factors of recurrence.102 Tumors of the extremity recurred more frequently and microscopic assessment of the surgical margin had no influence on recurrence.102,121 The high
recurrence rate after surgery suggests that a clinical trial of an adjuvant tolerable chemotherapy or other treatment shortly after surgery might be worthy of study in some cases.\textsuperscript{31} Adjuvant chemotherapy after surgery might be particularly useful after abdominal surgery in patients at high risk of DTF, such as patients with Gardner syndrome, although it has not been well studied.

In some cases radiation therapy can be useful\textsuperscript{97,103,112,122-127}, although radiation therapy has been reported to decrease local recurrence after marginal surgery in several uncontrolled studies, other retrospective studies have found no benefit.\textsuperscript{126} The role of radiation therapy among the various treatment options remains controversial because of long-term sequelae, including edema, pain, and second malignant neoplasm.\textsuperscript{4,19,94,97,103,112,116,121,123,128-131} In 1 study of 6 radiation-induced sarcomas in patients with DTF whose original tumor had a mutation in $\text{CTNNB1}$, 3 had the same $\text{CTNNB1}$ mutation as the original DTF, and 3 had no $\text{CTNNB1}$ mutation, suggesting that some cases of DTF were not derived from the original DTF tumor clone.\textsuperscript{132}

Cryoablation has also been used in an attempt to decrease the trauma associated with more extensive surgery, although its role remains to be defined.\textsuperscript{133}

Various medical therapies have been used for DTF, ranging from those with low toxicity such as nonsteroidal anti-inflammatory drugs\textsuperscript{4,18,134-136} or hormonal therapy\textsuperscript{9,18,31,137-140} to aggressive combination chemotherapy.\textsuperscript{9,18,134-136,158} Colchicine has also been used,\textsuperscript{140} and a case report suggests a possible response to 1,2-dihydroxyvitamin D$_3$.\textsuperscript{130} Comparative evaluation of different therapies is hindered by the fact that most case series are not randomized; the variable natural history of DTF further complicates the interpretation of these studies. In cases that respond to drug, the optimal length of treatment is unknown. Treatment approaches range from holding treatment at an arbitrary time in the setting of stable disease to prolonged treatment in responders, followed by abrupt cessation of therapy or gradually weaning treatment intervals or dose.

Magnetic resonance imaging (MRI) is the best imaging technique for diagnosis and monitoring of DTF.\textsuperscript{151-154} In some cases MRI may reveal changes associated with increased collagen deposition and decreased cellularity, such as a loss of T2 signal, suggesting either a response to treatment or a spontaneous decrease in disease activity.\textsuperscript{155,156} Changes in contrast enhancement may provide similar information.

Expression of estrogen receptor $\beta$ is often present and, along with the occasional relationship of DTF activity to pregnancy, provides some rationale for hormonal therapy.\textsuperscript{9,31,97,138-140,157-159} It has been reported that estrogen treatment can induce the formation of desmoid tumors that regress after discontinuing the drug or after adding progesterone.\textsuperscript{160} In 1 study of 25 patients with DTF (8 sporadic and 17 associated with FAP), a regimen of tamoxifen (120 mg/d) and sulindac (300 mg/d) was not highly effective in preventing DTF recurrence after surgery, but was still felt to be potentially useful in other settings, in which stable disease was the most common response.\textsuperscript{9} The optimal dose of tamoxifen for DTF is not well defined, and a range of doses has been used.\textsuperscript{9} Nonsteroidal anti-inflammatory drugs, typically ibuprofen or sulindac, have also been used with some efficacy.\textsuperscript{9,18,134-136,158} Desmoid-type fibromatosis also expresses androgen receptors; testosterone can stimulate DTF cell growth in vitro and DTF development in mouse models, suggesting androgen blockade as another potential hormonal approach.\textsuperscript{161}

A combination of methotrexate and vinblastine was one of the first chemotherapy regimens widely used for DTF, with response rates ranging from 30% to 50%.\textsuperscript{162-165} Because this regimen does have considerable toxicity, vinorelbine has largely replaced vinblastine in this regimen.\textsuperscript{166} Methotrexate combined with vinblastine or vinorelbine is more difficult to deliver over a prolonged course in adults because of toxicity.\textsuperscript{143,167} Other agents include more aggressive chemotherapy such as anthracyclines, gemcitabine, and even ifosfamide in rare cases.\textsuperscript{18,129,130,141,145-147,168,169} Tyrosine kinase inhibitors also have activity in some DTF cases, and meaningful responses have been described.\textsuperscript{64,153,156,160-174} In at least 1 case the tumor was responsive to sunitinib but not imatinib at the usual doses,\textsuperscript{165} suggesting that in some cases efficacy may be due to effects on targets other than KIT (kinase proto-oncogene receptor tyrosine kinase).
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Trials of tyrosine kinase inhibitors in DTF are ongoing (Table). Pegylated-liposomal doxorubicin (PLD) is particularly attractive, given its efficacy and low toxicity profile and is becoming widely used.18,120,130,169

Antibodies to WISP1 inhibit fibrosis in mouse models of bleomycin lung toxicity, suggesting this as a potential target for the future treatment of select cases of DTF as well. Similarly, the beneficial response of DTF to certain chemotherapy approaches suggests that a similar approach could be useful in severe cases of idiopathic pulmonary fibrosis. Altering Notch signaling with γ-secretase inhibition is also under study, and an adenosine monophosphate—activated protein kinase activator inhibits peritoneal fibrosis (a complication of peritoneal dialysis) in a mouse model.175 Preliminary data suggest activity of a γ-secretase inhibitor in DTF. Some ongoing trials for DTF are listed in the Table.

In some cases DTF tumors, and their constituent cells, may stabilize or regress, with a decrease in expression of biochemical markers of disease activity (Figure 4). The observation that DTF tumors sometimes stabilize or regress implies that the tumor myofibroblasts retain sensitivity to a regulatory system, likely an autocrine or more likely paracrine signaling system, similar to that of wound healing. That DTF tumors may still subsequently become active again after stabilization or regression implies that a population of cells remains that retains the ability to respond to some proinflammatory and/or profibrotic stimuli, in some cases induced by trauma, associated inflammation, or other physiological conditions, such as pregnancy. The degree to which recruited normal myofibroblasts contribute to the mass of clonal myofibroblasts in an individual DTF tumor could potentially affect the tumor behavior.

PREDICTING DTF BEHAVIOR
Predicting which treatment is most appropriate for a particular patient, such as the observation approach, would be useful. A nomogram using tumor size, location, and patient age has been reported to be useful in predicting recurrence after surgery.121 Some studies, but not all, have suggested that the location of the β-catenin mutation correlates with differences in clinical course of sporadic DTF. For example, tumors with S45F mutations in CTNNB1 may be at a higher risk of recurrence.40-42,45,49,53,56,102 One study found that DTF tumors with an S45 β-catenin mutation had a higher progression arrest rate than did wild-type tumors when treated with imatinib,176 and a European position paper encouraged β-catenin mutation testing in DTF.177 Another study found that higher nuclear β-catenin expression (>20% of tumor cells expressing nuclear β-catenin) had a higher recurrence rate than did lower expression.178 Trisomy 8 has also been associated with a higher risk of recurrence.179 In 1 study, immunohistochemical staining for ADAM12, Fap-1α, and WISP1 correlated with nuclear chromatin density and was higher in patients with an early recurrence (<1 year after surgery compared with no recurrence at 5 years).180 Other studies suggest that gene expression patterns may also correlate with biological behavior48,51,180,181 and might be useful in identifying patients who would more likely benefit from therapy.

DESmoid-TYPE FIBROMATOSIS AS A MODEL FOR THE ROLE OF TUmOR stROMA IN OTHER DISEASEs
The tumor stroma in invasive carcinomas frequently exhibits a desmoplastic response with proliferation of myofibroblasts, and tumors have been described as "wounds that do not heal."5182,p1690 Fibroblasts and myofibroblasts in neoplasms can secrete various trophic, mitogenic, and proinflammatory growth factors including hepatocyte growth factor, epidermal growth factor, TGF-β, and insulin-like growth factor 1 (reviewed in reference 183), possibly influencing growth of the clonal neoplastic cells. Because of their potential contribution to tumor biology, targeting the normal stromal myofibroblasts in tumors is an interesting potential approach to cancer treatment.184 As DTF closely resembles wound healing, it may be a potentially useful model to study the role of tumor stroma. Indeed, some studies suggest that gene signatures similar to that seen in DTF correlate with clinical outcome in some malignancies.184,185-188 Desmoid-type fibromatosis may also provide a model for
other fibrosing diseases such as progressive pulmonary fibrosis.

**DESMOID-TYPE FIBROMATOSIS CASE EXAMPLES**

As described above, DTF can have a different course in different patients. Thirteen cases of DTF are summarized here (10 in Supplemental Materials, Supplemental Figure 2, available online at [http://www.mayoclinicproceedings.org](http://www.mayoclinicproceedings.org)) to illustrate important principles of DTF biology and treatment.

**Case 1: Slow Spontaneous Regression of an Extra-Abdominal DTF in a Man**

A 28-year-old man noted a small mass in his right chest near the sternum. He developed psoriatic arthritis 8 months later and began treatment with methotrexate. A year after initiating methotrexate, etanercept was added. At presentation 8 months after starting etanercept, he was not sure the mass had grown over the past year, but he now had occasional twinges of pain lasting a few seconds, from none to several times a day. Thus, the tumor progressed symptomatically while on methotrexate. Examination revealed a firm, fixed, nontender parasternal mass. Computed tomography revealed a mass involving the sternum growing through the chest wall (Figure 5, top panel) and a biopsy revealed DTF. Consultation at another institution recommended surgical removal of the chest wall mass; however, he was observed, and 3 months later his symptoms and imaging of the mass were unchanged. Ten months after the biopsy, the mass was slightly smaller and symptoms were unchanged. At 35 months after the biopsy, his symptoms had resolved and the mass was smaller (Figure 5, bottom panel). He remains symptom free 50 months after the biopsy and continues the observation. This case exhibits slow spontaneous regression of an extra-abdominal DTF in a man, not related to estrogen.

**Case 2: DTF Caused by Local Trauma/Inflammation and Stable Disease After Methotrexate and Vinblastine**

A 33-year-old man presented with a painful mass in the arm. He had an influenza shot 1.5 years before presentation, and shortly thereafter he became aware of a persistent discomfort in the region of the injection site that gradually progressed, and a painful mass developed. The size of the mass and degree of pain progressed markedly over the 2 months before presentation. Examination revealed a slightly tender warm 10 cm hard mass fixed to the underlying tissue in the proximal right arm. Magnetic resonance imaging revealed a 7 × 5 × 8.5 cm mass along the triceps muscle that was hyperintense on a fluid-sensitive image with some areas of heterogeneity (Supplemental Figure 1, available online at [http://www.mayoclinicproceedings.org](http://www.mayoclinicproceedings.org)). A tru-cut biopsy revealed DTF, and an open biopsy performed to exclude a low-grade sarcoma also revealed DTF. Surgical treatment was felt to require shoulder disarticulation. As surgical treatment was felt to result in significant morbidity, chemotherapy with methotrexate and vinblastine was begun. At 6 weeks of treatment, there was no clear evidence of change in tumor size or symptoms, and he moved to a different state in which chemotherapy was continued for 2 more months without change in tumor size. The tumor was then surgically excised. He was sent for consideration of postoperative radiation therapy and thereafter lost to follow-up. This case exhibits DTF development after local trauma/inflammation, potential significant morbidity of treatment (shoulder disarticulation or more limited disfiguring surgery), and disease stabilization with methotrexate and vinblastine.

**Case 3: Aggressive Multifocal DTF Controlled With PLD**

A 32-year-old man with Gardner syndrome presented with painful extra-abdominal desmoid tumors as well as large intra-abdominal desmoids requiring opiates. He also had a pulmonary embolus and venous thrombosis and was taking coumadin. He had been treated a year earlier with tamoxifen for 8 weeks, but tumors grew during this period. He began treatment with PLD and had a good response. Treatment was held after 6 cycles. Desmoid-type fibromatosis progression was noted 10 months after the last chemotherapy, and he received imatinib 400 mg/d orally, but it progressed. He began treatment with PLD and noted stabilization of pain after 1 month and some tumor shrinkage at 3 months. Three months later, imaging revealed further tumor regression, and the interval between PLD treatments was increased. Subsequent imaging
revealed continued gradual tumor shrinkage and then stabilization, and PLD was discontinued after 1.5 years of treatment. Imaging found stable disease at 3 years after reinitiating PLD, but 4 months later (40 months after first initiating chemotherapy) he developed increasing pain and progression of DTF on imaging, and PLD was reinitiated. One month later he developed small bowel obstruction, bacteremia, and renal failure and had a decompressive gastrostomy tube placed. His subsequent course was complicated, and he eventually entered a hospice program and died 5.3 years after initial chemotherapy. This case exhibits aggressive multifocal DTF, long-term control with PLD, and severe DTF-associated morbidity.

**FUTURE STUDIES**

Controlled trials are needed to better define optimal treatment approaches. Future clinical trials must consider several aspects of DTF biology. First, because of the highly variable clinical course of DTF, patients must be carefully stratified at entry. Factors to consider include rate of tumor growth (tumor growth rate should be quantitated before treatment). Other stratification variables should include age at diagnosis, tumor location (mesenteric, abdominal wall, central extra-abdominal, and extremity), β-catenin mutation and APC mutation status, relation to pregnancy, symptoms, and tumor size. Samples should be obtained for future, more detailed genetic analysis; consideration should be given to obtaining core biopsies from different parts of the tumor; if possible, given the known intratumoral variability. Watchful waiting should be the first treatment, if possible, and when treatment is initiated, randomization to 2 treatments is needed. The “standard” treatment can be debated, but given its efficacy, tolerability, and increasing popularity, PLD would be one consideration. Finally, a decision on how long to treat a responding tumor and how to quantify tumor response must be considered. RECIST (Response Evaluation Criteria In Solid Tumors) is known to be a poor measure of response in DTF, but some measure of size (optimally careful analysis of tumor volume) and tumor “activity” (possibly determined by

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**FIGURE 5.** Slow spontaneous regression of an extra-abdominal desmoid-type fibromatosis (DTF) in a man. A 28-year-old man developed a firm, fixed, nontender parasternal mass. Computed tomography revealed a mass involving the sternum growing through the chest wall (top panel), and a biopsy revealed DTF. He was observed, and 10 months after the biopsy the mass was slightly smaller. At 35 months after the biopsy, his symptoms had resolved and the mass was smaller.
contrast enhancement or changes in T1/T2 signal on MRI) need to be considered. Because tumor stabilization can be a beneficial outcome, a measure of symptoms experienced by the patient should be included as well, including a quality of life assessment such as QLQ-C30 or FACTG. Perhaps better than nonlinear subjective variables such as a “pain scale” are clear measures such as the following: is a pain medication required, how much pain medication is used, does the tumor interfere with sleep (yes/no), how far can the patient walk before tumor pain limits the activity (this could be objectively determined at each clinic visit for cases with serious symptoms), and what is the range of motion of the affected body part. Only with carefully controlled trials that use careful stratification based on known variables can the best treatment approaches for DTF be determined.

SUMMARY

Because of the heterogeneity of the biological behavior of DTF, the optimal approach to treatment is unclear. Historically, surgery was the mainstay of treatment, but recurrence after treatment is unclear. Historically, surgery was the mainstay of treatment, but recurrence after treatment is unclear. Surgery has become more standard. Although surgery remains an option for the associated mesenteric DTF.

CONCLUSION

Desmoid-type fibromatosis is an uncommon locally invasive tumor. Because of the variable nature of the disease and the potential morbidity of treatment, some cases of DTF may do better without treatment; simple observation is often the best initial treatment.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms. APC = adenomatous polyposis coli gene; CK1 = casein kinase 1; DTF = desmoid-type fibromatosis; ECM = extracellular matrix; FAP = familial adenomatous polyposis; Fap-1α = fibroblast activation protein 1α; GSK3 = glycogen synthase kinase 3; MRI = magnetic resonance imaging; PDGF = platelet-derived growth factor; PDGF-Rα = platelet-derived growth factor receptor-α; PLD = pegylated-liposomal doxorubicin; TGF = transforming growth factor

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