MAYO CLINIC

REVIEW

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.[1-8] However, although uncommon, DTF may be multifocal. The word *desmoid* derives from the Greek *desmos* meaning "bandlike, bond, or fastening."[9,10] Desmoid-type fibromatosis was originally described by McFarlane in 1832[11] and termed "desmoid tumor" by Mueller in 1838. By 1904, about 400 cases had been reported.[10-13] The term *fibromatosis* was later introduced by Stout.[14] 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.[3] Trauma is a common inciting agent for the development of DTF,[3,15-17] 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.

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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.[18,19] The incidence of DTF is about 2

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.

to 4 per million per year in the general population.[20-23] 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.[24-26] 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.[9,27-29] Desmoid-type fibromatosis develops in approximately 5% to 30% of patients with FAP, usually in the mesentery.[20,21,25,30-32] In some studies, FAP-associated DTF represents about 2% of DTF cases[9]; in 1 Dutch study, nearly 10% of patients with DTF have or will develop FAP.[21,33] 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.[32,34,35] Kindreds of familial DTF without the colonic features of FAP have also been reported in which mutations occur in a different region of *APC*.[36,37] Genetic predisposition to DTF in patients with FAP independent of germline *APC* mutation has also been described, suggesting the existence of genes independent of *APC* that influence DTF formation in FAP.[38] Although common in patients with FAP, most cases occur sporadically in young adults[15,18] and are associated with a mutation in β-catenin (*CTNNB1*).[19,39-44] Desmoid-type fibromatosis and a related disease, infantile aggressive fibromatosis, may also differ between children and adults.[45,46] 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 circumscribed 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 (Figure 1, A). 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.[47,48] Cells with more euchromatin are presumably more "transcriptionally active," whereas cells with more heterochromatin are felt to be more "transcriptionally inactive."[47] 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.[48] Figure 1, C, from the same tumor shows an area that appears histologically active, characterized by cells with plump, light-staining oval nuclei,

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