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ScienceDirect
EJSO 35 (2009) 3–10
EJSO the Journal of Cancer Surgery
www.ejso.com

Review

The role of APC and beta-catenin in the aetiology of aggressive fibromatosis (desmoid tumors)

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Accepted 9 July 2008
Available online 21 August 2008

Abstract

Background: Aggressive fibromatosis (syn. desmoid tumor) is a sporadically occurring neoplastic proliferation of fibroblasts originating from musculoaponeurotic planes, forming invasively growing masses without the capability to metastasize. The choice of treatment remains surgical resection with or without radiotherapy, and is characterized by high recurrence rates. Better understanding of the aetiology of aggressive fibromatosis is needed to be able to develop new treatment strategies to cope with the high recurrence rates.
Methods: Relevant studies were identified through a search of the electronic databases PubMed/ Medline. The following search terms were used: 'aggressive fibromatosis', 'desmoid tumor', 'adenomatous polyposis coli', 'APC', 'beta-catenin', 'Wnt', 'Wingless' and 'Wnt/Wingless'. Studies were selected for review on the basis of abstract reading. A hand search was performed by checking reference lists in selected articles.
Results: The neoplastic nature of aggressive fibromatosis and the role of the adenomatous polyposis coli (APC) and β-catenin signaling cascade in driving the onset and progression of this disease are discussed.
Conclusion: Mutations in either the APC or β-catenin genes are likely to be a major driving force in the formation of these desmoid tumors. More research is needed to develop new treatment strategies.

Keywords: fibromatosis, aggressive; desmoid tumor; adenomatous polyposis coli; β-catenin

Introduction to aggressive fibromatosis

Epidemiology and histology

Aggressive fibromatosis (syn. desmoid tumor) is an infrequently occurring invasively growing tumor lacking the capability to metastasize. The incidence of occurrence in the general population is two to four new patients per million.[1] In relation to other malignancies, the incidence is 0.03% of all newly diagnosed neoplasms and 3% of all soft-tissue malignancies.[2] Desmoid tumors are neoplastic in nature, but there is no consensus in international literature in classifying these tumors as benign or malignant. They possess aggressive and infiltrative capacities, but lack the common characteristic of malignancies, i.e. metastases. The desmoid tumor is histopathologically characterized by a heterogeneous, poorly circumscribed, infiltrating mass consisting of uniform elongated spindle cells (fibroblasts-like) surrounded by abundant collagen fibers. The spindle-shaped cells have little cytological atypia and mitosis is rarely observed. The tumor originates from musculoaponeurotic planes and is found intra- and extra-abdominally. Extra-abdominal desmoid tumors are mainly seen at the pelvic and shoulder girdles, upper and lower extremities and paravertebral.[3] Additionally, multiple case reports have reported aggressive fibromatosis also at uncommon locations such as the female breast.[4] Aggressive fibromatosis is predominantly

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doi:10.1016/j.ejso.2008.07.003

diagnosed as a sporadically occurring tumor. However, its occurrence is also seen in hereditary syndromes such as familial adenomatous polyposis (FAP), hereditary desmoid disease (HDD) and familial infiltrative fibromatosis (FIF) (see Table 1).[1,5,6] It has also been observed that aggressive fibromatosis is often the first presentation of familial adenomatous polyposis.[7,8]

In this article we reviewed the existing literature concerning the aetiology of both sporadic and hereditary aggressive fibromatosis. We discuss the neoplastic nature of aggressive fibromatosis and the role of the adenomatous polyposis coli (APC) and β-catenin signaling cascade in driving the onset and progression of this disease.

Treatment

The preferred modality of treatment is surgery with tumor-negative margins, with or without radiotherapy.[9,10] The treatment of desmoid tumors is, however, unfortunately characterized by high recurrence rates. Local recurrence has been reported to be as high as 40–60% and clinically present within 2 years of primary resection.[10]

In large patient series from high volume centers the outcome of surgical resection improved in recent years and recurrence rates decreased.[11] This improvement is not completely explained by better surgical treatment as defined by lower margin-positive resection percentages. A better explanation is the introduction of combined treatment, such as adjuvant radiotherapy or systemic therapy. The latter is not a optional treatment modality by itself for aggressive fibromatosis. Systemic therapy, either by chemotherapy or hormonal therapy, has not been able to effect a partial or complete response in the majority of patients.[12,13] Most patients show stabilization of disease or disease progression, resembling the natural course of disease. The role of hormonal therapy is even more disputable. Estrogen and progesterone receptors are found in a minority of tumor specimens; in large cohort studies there are no associations between female sex and desmoid tumor incidence; and hormonal therapy has not been adequately tested in randomized controlled trials.[11,14–16] Moreover, to our knowledge there are no relevant associations observed between estrogen-related intracellular signaling pathways and the Wnt/Wingless pathway. The choice of treatment remains surgical resection with or without radiotherapy, and future well-designed randomized controlled trials should be performed to improve our knowledge about aggressive fibromatosis therapy.

Table 1
Types of aggressive fibromatosis

Sporadic disease			
Sporadic (idiopathic) aggressive fibromatosis	Somatic mutations APC and/or β-catenin		• Variable phenotype
Inherited disease			
Familial adenomatous polyposis (FAP)	Germline mutations APC	10–15% penetrance	• Predominance of GI disease in clinical phenotype • Late onset (3rd–4th decade) • Mainly mesentery
Familial infiltrative fibromatosis (FIF)/ Hereditary desmoid disease (HDD)	Germline mutations APC	~100% penetrance	• Predominance of desmoid disease in clinical phenotype • Early onset (1st–2nd decade) • Mainly in proximity axial skeleton

APC, adenomatous polyposis coli; GI, gastrointestinal.

The neoplastic nature of aggressive fibromatosis

These tumors cause loss of function of organs they invasively grow into, thereby potentially causing mortality when the functions of vital organs are impaired. They are often classified as benign neoplasms with infiltrating growth because of their low mitotic activity, the absence of metastases, and the occasionally observed spontaneous regression.[17] In line with this assumption they are sometimes referred to as *deep fibromatoses*, in contrast to *superficial fibromatoses* which include palmar, plantar and penile fibromatosis (resp. Dupuytrens' or Lederhosen contracture and Peyronie's disease). They are also considered to belong to the group of reactive fibrous proliferations and nodular fasciitis.[18] Aggressive fibromatosis has an osseous equivalent called desmoplastic fibroma, which displays an identical histological pattern and is regarded as a benign tumor.[19]

Desmoid tumors harbor pure malignant capacities and could be categorized within the spectrum of fibroblastic malignancies including graded (i.e. low- and high-graded) fibrosarcomas.[20] The clonal nature of aggressive fibromatosis is indicative of neoplasia.[17] The strongest evidence for neoplasia is provided by multiple studies describing the clonal nature of desmoid tumors. Some of these studies investigated the clonal nature through analyses of trisomy 8 and/or 20 in tumor specimens, which are non-random clonal aberrations acquired during neoplastic progression. It has even been suggested that the presence of trisomy 8 could be a predictor of recurrence.[21,22] However, these clonal aberrations have also been observed in benign proliferations such as superficial fibromatosis, solitary benign fibrous tumors and (osteo)fibrous dysplasias.[21,23] Furthermore, the presence of trisomy 8 and/or 20, and the proportion of cells with these trisomies (i.e. clonality ratio) vary greatly between tumor specimens, ranging from 0–25% and 2–25% respectively.[21,23] It is therefore more accurate to conclude that trisomies 8 and 20 contribute to aberrant neoplastic cell proliferation in a wide spectrum of pathologic fibrous proliferations, without making a distinction between benign or malignant.

The clonal nature of desmoid tumors has also been investigated by examining the occurrence of non-random