Desmoid Tumors

A Comprehensive Review of the Evolving Biology, Unpredictable Behavior, and Myriad of Management Options

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KEYWORDS

• Desmoid • Aggressive fibromatosis • Review • Familial adenomatous polyposis
• Tyrosine kinase inhibitors

KEY POINTS

- Desmoid tumors are rare tumors of mesenchymal origin that vary widely in presentation and behavior.
- Desmoid tumors can occur in association with familial adenomatous polyposis, trauma, prior surgery, or pregnancy.
- Sporadic desmoid tumors can be associated with somatic mutations in the β-catenin gene.
- Many treatment modalities have shown benefit ranging from conservative, nonsurgical approaches to aggressive cytotoxic chemotherapy.
- Ongoing studies on the biology of desmoid tumors are leading to more potential rational therapeutic strategies.

INTRODUCTION

Desmoid tumors, also known as aggressive fibromatosis, were first coined in the 1830s after the Greek word *desmos* meaning "tendon-like." These rare tumors arise from mesenchymal cells, similar to their malignant counterpart, sarcomas. Unlike sarcomas, there is no metastatic potential for desmoid tumors. However, despite their

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benign classification, desmoid tumors can be multifocal, and locally infiltrate surrounding structures such that they can be a cause of both significant morbidity and, rarely, mortality.

Desmoid tumors vary widely in presentation and behavior. These collections of fibrous tissue range from being relatively indolent and asymptomatic to creating severe local symptoms with significant morbidity. Accordingly, treatments range in aggressiveness and include observation, surgery, radiation therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), hormonal agents, tyrosine kinase inhibitors (TKIs), and cytotoxic chemotherapy. New molecular insights into desmoid tumors suggest potential therapeutic targets in an attempt to expand the arsenal of therapeutic options.

EPIDEMIOLOGY

Desmoid tumors are uncommon, with an estimated incidence of 2.4 to 4.3 per million per year,[1] accounting for less than 3% of soft-tissue lesions.[2] Although there is some variability, there is a 2- to 3.5-fold increased incidence in women.[3,4] A wide range of ages is affected, with most cases occurring between the ages of 15 and 60 years with an average age of 36.7 years.[4] The majority of cases are sporadic with no known predisposing factors. However, a sizeable minority of desmoid tumors occur as a consequence of the genetic syndrome familial adenomatous polyposis (FAP) or in association with pregnancy or trauma (see the section on predisposing factors).

PATHOGENESIS

The Wnt/β-catenin pathway drives the pathogenesis of both sporadic and FAP-associated desmoid tumors. FAP-associated tumors frequently have adenomatous polyposis coli gene (*APC*) mutations at or beyond 3′ of codon 1444.[5–9] One function of APC is to regulate the protein level of β-catenin. When β-catenin is present in high concentration it binds to APC, followed by binding of the serine-threonine kinase GSK3β. This binding eventually leads to phosphorylation of sites on APC and β-catenin degradation.[10,11] In cases of mutated *APC* a truncated APC protein is created, which is unable to degrade β-catenin appropriately.[11] This process results in accumulation of β-catenin and its target genes, which are implicated in loss of proliferation regulation.[10]

Approximately 85% to 90% of sporadic desmoid tumors are associated with somatic mutations in the β-catenin gene, *CTNNB1*.[12–14] In a study of 254 cases of sporadic desmoids, 88% had *CTNNB1* mutations identified by direct sequencing, compared with no mutations detected in the control of 175 other spindle-cell lesions.[13] These gene mutations have been found in codons 41 and 45 of exon 3 of *CTNNB1*, which produce a stabilized β-catenin protein product leading to an accumulation of β-catenin in the cell.[15]

In endothelial cells β-catenin is not only a cell-adhesion molecule, but also plays a role in nuclear transcription.[16] Accumulation of β-catenin, by constitutive activation of the Wnt ligand pathway, loss of APC protein function, and inability to phosphorylate β-catenin or mutations in the *CTNNB1* gene, allows translocation of cytoplasmic β-catenin into the nucleus and, in conjunction with other proteins, promotes abnormal proliferation.[15,17]

Recognizing the central role of β-catenin in desmoid tumors, the current value of *CTNNB1* evaluation in an individual patient is unclear. Some advocate that pediatric desmoid patients with β-catenin accumulation in the nucleus be evaluated for the presence of *CTNNB1* mutation. If negative, APC mutation analysis should be considered, as this could potentially be the initial manifestation of FAP.[18,19] Evaluation of