Management of Desmoids

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KEYWORDS

• Desmoid fibromatosis • Beta-catenin • Management • Margins • Observation

KEY POINTS

- Desmoid fibromatosis is an infiltrative tumor that can be aggressive in nature because of its ability to locally invade adjacent structures.
- Mutations in β-catenin and APC genes are responsible for the development of most desmoid tumors.
- Wide local excision with negative margins is the standard surgical treatment of desmoid tumors.
- A variety of nonsurgical therapies are useful in the management of desmoid tumors, including radiation, chemotherapy, nonsteroidal antiinflammatory drugs, and hormonal therapy.
- Treatment algorithms are evolving with the observation that many tumors remain stable under a program of watchful waiting, and spontaneous regression has been observed.

INTRODUCTION

Desmoid tumors (also known as aggressive fibromatosis) are rare, with an incidence of 0.03% of all neoplasms and 3.0% of soft tissue tumors.[1] They are seen more commonly in women than men with a 2:1 predilection for women.[2–4] Young adults are the most commonly affected, and it is frequently in the 25- to 35-year-old demographic.[2,3] Most desmoid tumors occur sporadically, but they can be associated with familial adenomatous polyposis syndrome (FAP). In the FAP patient population there is not a sex predilection for these tumors.[5] Mutations in either the β-catenin or APC genes are usually the cause for the development of these tumors. Sporadic development of desmoid tumors has been associated with β-catenin mutations, whereas mutations in the APC gene pathway are associated with development of desmoids in the setting of FAP syndrome. It seems that these mutations are mutually exclusive.[6] Other factors that have been associated with development of desmoids include

Disclosures: none.
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Surg Clin N Am 96 (2016) 1015–1030
http://dx.doi.org/10.1016/j.suc.2016.05.008 **surgical.theclinics.com**
0039-6109/16/$ – see front matter

pregnancy, hormonal exposure, and physical factors, such as trauma and/or surgery.[3,4] Although desmoid tumors cannot be considered a true malignancy because of their inability to metastasize, they are aggressive in their ability to locally invade adjacent structures. Surgical resection has been the mainstay of treatment; however, recurrence rates range from 20% to 45%.[7–9] Because of the propensity for recurrence, multimodal therapies have been used, including hormonal therapy, nonsteroidal antiinflammatory drugs (NSAIDs), chemotherapy, and radiation. Recently the surgery-first approach has begun to evolve into a movement of watchful waiting, as observational studies have shown long-term stability of some tumors without treatment and even spontaneous regression in 5% to 10%[6,10] of cases.

Pathogenesis

Alterations in the Wnt signaling pathway seem to be the mechanism of tumorigenesis in the development of desmoid fibromatosis.[11] Genetic mutations that alter this pathway and are associated with the development of desmoid tumors have been identified in the β-catenin and APC genes. Both β-catenin and APC are part of the Wnt pathway suggesting that 2 separate mutations affecting the same end point are involved with the development of desmoid fibromatosis.[12] These mutations result in the development of intranuclear accumulation of β-catenin, which stimulates DNA transcription and cell proliferation.[11] Eighty-five percent of sporadic desmoid tumors have an activating mutation in the CTNNB1 gene coding for β-catenin, whereas the germline mutation of the APC gene leads to the development of desmoid tumors for patients with FAP.[11,13] More recently a genetic analysis looking at wild-type desmoids or those without the aforementioned known mutations found that with deep sequencing 95% of desmoids may have mutations that affect the Wnt/β-catenin pathway suggesting a near-universal relationship between desmoid tumors and the Wnt signaling.[14]

In sporadic desmoid tumors, mutations in the gene coding for β-catenin, CTNNB1, occur in 71% to 91% of tumors. The highest rate of mutation is found in intra-abdominal tumors.[13,15–19] The most common mutations are T41A and S45F. The discovery of genetic mutations in the development of desmoid tumors has been an important advancement as they have also been associated with prognosis, providing the opportunity to improve the ability to risk stratify patients. Several studies have shown a significantly higher chance of disease recurrence at 5 years despite complete resection for patients harboring a S45F mutation, which is likely exclusive to extra-abdominal desmoids.[13,17,19] The growing amount of data suggests that specific mutations within this gene do play a role in disease recurrence and provide the opportunity to influence clinical care in the future.

For those without a β-catenin gene mutation, APC gene mutations are suspected to be the source of development of desmoid tumors. APC mutations are most common among patients with FAP. Approximately 10% to 15% of patient with FAP develop desmoids, and intra-abdominal tumors have become the primary cause of death in patients with FAP who have previously had a prophylactic colectomy.[11,20] Despite a similar molecular end point for APC and β-catenin mutations, the phenotype between the two is different, as most tumors in FAP are intra-abdominal with involvement of the small bowel mesentery.[5]

Presentation

Desmoid tumors can occur anywhere in the body. They are divided into 3 general anatomic locations: extra-abdominal, intra-abdominal, and abdominal wall. There