

Abdominal Pain and Colonic Obstruction From an Intra-Abdominal Desmoid Tumor

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Desmoid tumors are rare, benign, slow-growing, fibroblastic neoplasms that originate from musculoaponeurotic and fascial structures throughout the body. These tumors do not have the ability to metastasize, but they are locally aggressive, with a high rate of recurrence even after surgical resection. Desmoids can cause severe clinical sequelae, including mortality due to infiltration of nearby organs. In this case report, we discuss a patient who presented with right lower quadrant abdominal pain and extraluminal colonic obstruction secondary to a desmoid tumor.

Case Report

A 46-year-old woman with a past medical history of rheumatoid arthritis, who was on weekly methotrexate therapy, presented to her primary care physician complaining chiefly of right lower quadrant abdominal pain of 4 weeks' duration. She described the pain as a progressive, dull ache lasting over the preceding 6 months, with intermittent episodes of sharp, severe pain. The pain occasionally radiated to the back and left lower quadrant, but it generally remained in the right lower quadrant. The patient experienced some associated nausea but denied having any associated vomiting, constipation, diarrhea, hematochezia, or weight loss. She had tried taking over-the-counter analgesics and, eventually, simethicone and hyoscyamine (Levsin, Schwarz Pharma), as prescribed by her primary care physician. At a follow-up visit 6 months later, the patient reported no relief with the above therapies and was experiencing progressive symptoms of dull pain and pressure in the right lower quad-

rant. Her past medical history was significant for a tonsillectomy as a child and for rheumatoid arthritis, which had been diagnosed in 2005 and for which she was receiving weekly methotrexate injections (20 mg/wk). Besides methotrexate, she was also taking folic acid. Her family history was significant for gallstones and kidney stones, but she did not have any history of autoimmune diseases, inflammatory bowel disease, or malignancy. She did not use tobacco, alcohol, or recreational drugs.

On examination, the patient was afebrile with stable vital signs. She was alert and in no acute distress. Her conjunctivae were anicteric, her mucus membranes were moist, and her oropharynx was clear. She had a normal thyroid examination and no cervical or supraclavicular lymphadenopathy. Her lungs were clear to auscultation, and her heart showed regular rhythm with no murmurs, rubs, or gallops. Abdominal examination revealed a normal-appearing abdomen, which was nontender, nondistended without any peritoneal signs of rebound or guarding, and without appreciable hepatosplenomegaly. Bowel sounds were present in all 4 quadrants. The remainder of her examination was unremarkable.

Given the progressive nature of her symptoms, a computed tomography (CT) scan of the abdomen and pelvis was ordered with oral and intravenous contrast. The CT scan revealed a 6.4-cm × 3.1-cm soft-tissue density adjacent to the ascending colon (Figure 1). Circumferential wall thickening of the adjacent ascending colon was seen, as was a left adnexal mass measuring 4.0 cm × 3.1 cm, which was consistent with an ovarian cyst. Otherwise, the remainder of the examination was unremarkable. The radiologist proposed that the right lower quadrant mass represented an ascending colon neoplasm with adjacent lymph node enlargement or a primary extracolonic mass. Colonoscopy was thus recommended and revealed a 5-mm polyp in the transverse colon and an

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Figure 1. Computed tomography scan revealing a right lower quadrant mass adjacent to the ascending colon (arrow).



Figure 2. Impassable segment of the ascending colon seen during colonoscopy.

impassable segment in the mid- to distal ascending colon, corresponding to the location of the abnormality on the patient's CT scan (Figure 2). The endoscopist noted a twist in the bowel at this segment, which raised concerns for a possible chronic cecal volvulus. A barium enema study was ordered to further evaluate these findings.

Despite multiple maneuvers by the barium technician, contrast did not reach the cecum. The barium enema study confirmed that this obstruction was secondary to a very irregular and narrowed colon in the region of the hepatic flexure and ascending colon, with associated dilation of the proximal bowel (Figure 3). Based upon the study, it was not possible to determine whether this finding was caused by an intraluminal growth or extrinsic compression. Given these findings, the patient was referred for surgical evaluation for definitive diagnosis and possible resection.

The patient underwent incisional biopsy of the mass and subsequent right hemicolectomy with ileocecectomy, appendectomy, and associated removal of pericolic fat and mesentery, which included the mass in question. The gross specimen included a 6.2-cm × 6-cm × 3.7-cm well-defined, tan white, firm, trabecular, and slightly whorled mass that was completely free of surgical margins (Figure 4). The mass grossly extended to involve the serosal and muscularis layer of the right colon but did not grossly involve the mucosa. On histologic evaluation, the mass consisted of fibroblastic proliferation with generally low cellularity, bland cytology, and no appreciable mitotic activity. The mass was also densely collagenized. The



Figure 3. Barium enema study revealing obstruction of the ascending colon (arrow) caused by either an intraluminal or extracolonic mass.

tumor cells stained positive for desmin and beta-catenin but negative for CD34, CD117, S-100 protein, and keratin AE1/3, which was consistent with a diagnosis of desmoid tumor (fibromatosis).

The patient tolerated the procedure without complications. At a follow-up visit 3 months later, she reported

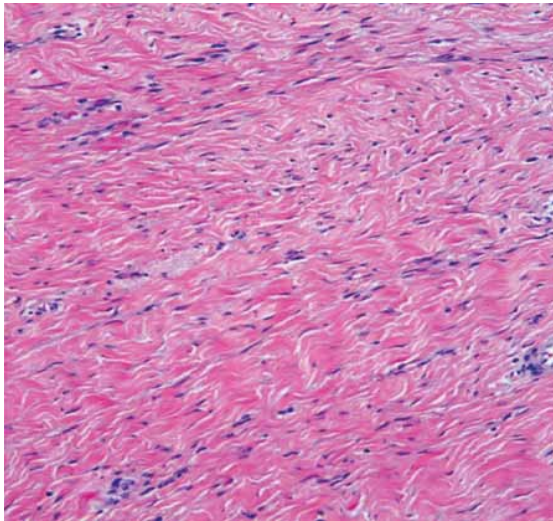


Figure 4. Desmoid tumor with fibroblastic proliferation, low cellularity, and dense collagenization (hematoxylin and eosin stain).

complete resolution of her right lower quadrant pain. Plans for further follow-up included serial clinical and radiographic evaluation (CT scans) every 6 months.

Discussion

In this case report, our patient presented with right lower quadrant abdominal pain of 6 months' duration, and work-up eventually revealed a desmoid tumor. These tumors typically appear as well-differentiated growths of fibrocollagenous tissue that are locally infiltrative and aggressive. Although they do not have malignant potential or the ability to metastasize, their aggressive nature often causes significant morbidity and mortality due to infiltration of vital organs and structures.¹ Given their tendency to recur after resection or medical management, desmoid management can be quite challenging for clinicians.

Pathophysiology

The cell of origin for desmoid tumors is the myofibroblast, which explains their typical occurrence in musculoaponeurotic tissue. The currently understood mechanism for development of desmoid tumors involves mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q. The *APC* gene codes for the beta-catenin binding/degradation protein (APC protein). Beta-catenin is responsible for activating transcription factor Tcf-4, an important protein involved in fibroblast proliferation. The APC protein prevents accumulation of beta-catenin by mediating its phosphorylation and degradation.² Thus, mutations in the *APC* gene result in beta-catenin over-

expression and resultant dysregulation of mesenchymal and fibroblast cell proliferation and invasiveness.³ This explains the high rate of desmoid occurrence in patients with familial adenomatous polyposis (FAP) or Gardner syndrome. These disorders, known to cause early and aggressive development of colorectal adenomatous polyps and cancer as well as soft- and hard-tissue neoplasms, are secondary to point mutations in the *APC* gene. Up to 20% of patients with FAP may be afflicted by desmoid tumors.⁴ Similarly, patients who have had previous surgery or antecedent trauma are at increased risk for desmoid development, as beta-catenin levels are elevated during the proliferative phase of wound healing.⁵ Alternatively, a link has been postulated between desmoid development and high estrogen states such as pregnancy, as estrogen has been shown to promote fibroblast proliferation.⁶

Epidemiology

Desmoid tumors are extremely rare, causing 0.03% of all neoplasms and less than 3% of all soft-tissue tumors. They typically develop in young and middle-aged adults (10–60 years of age) but can be occasionally found in young children as well as the elderly. There is a slight female predominance with this disease, but no racial or ethnic trends have been observed.⁷

Clinical Presentation

Given the extensive distribution of musculoskeletal and stromal tissues, desmoids can arise almost anywhere in the body. However, there are several common sites of development: the trunk and extremities (usually the shoulder or pelvic girdle), the abdominal wall (typically arising from the rectus muscle), and inside the abdomen (from the bowel or mesentery). Depending upon the location, most desmoids present as slow-growing, painless (or minimally painful) masses. Intra-abdominal desmoids may cause bowel obstruction or ischemia, whereas extremity desmoids may cause nerve entrapment or lymphatic obstruction. Given the slow-growing nature of intra-abdominal desmoids, pain associated with these tumors typically indicates significant visceral involvement.⁸ Due to a link with wound healing, sites of prior trauma or surgery are often involved. On examination, the typical finding consists of a firm, smooth, and mobile mass that is adherent to its surrounding structures. Usually, the overlying skin is not affected.

Diagnostic Evaluation

Initial work-up typically consists of imaging of the affected anatomic site to confirm the cause. Although both CT and magnetic resonance imaging (MRI) are adequate for evaluation, MRI is preferred, particularly for extremity desmoids, as it better reveals involvement of surround-

ing tissues. As neither imaging modality can distinguish a desmoid from a malignant soft-tissue tumor, histologic evaluation is needed to confirm the diagnosis. A biopsy can confirm monoclonal growth of fibroblast cells, which appear as a bundle of spindle cells in a fibrous stroma. Cellularity is typically low. Distinguishing desmoids from fibrosarcomas is particularly important and necessitates an incisional biopsy, rather than fine-needle aspiration. Pathologically, this is accomplished by observing that the cells in the desmoids lack nuclear and cytoplasmic features of malignancy (ie, there are few mitotic bodies, and necrosis is absent). Immunohistochemical staining can aid in the process of diagnosis, as can nuclear beta-catenin staining. Additionally, spindle cells often contain vimentin and smooth muscle actin but rarely stain for desmin, cytokeratins, and S-100.⁹

Treatment

Early referral to a center that specializes in multimodality care of sarcomas is warranted. In asymptomatic patients, close observation is often the preferred strategy. Patients with symptoms are typically treated, given the inevitably progressive growth of desmoid tumors. Surgery with a wide margin of resection is the preferred treatment whenever feasible, particularly for intra-abdominal desmoids.¹⁰ Limitations include tumor involvement of vital anatomic structures, where resection would lead to functional limitation or significant morbidity and mortality. Similarly, desmoids frequently recur at a high rate (16–39%), even when surgical margins are free of tumor, and these recurrences are often more aggressive than the initial tumor.¹¹

Radiation therapy has been shown to be an effective alternative for definitive care in patients who refuse surgery, patients who are not good surgical candidates, or patients in whom surgery carries a high risk.¹² Additionally, trials are being conducted to evaluate neoadjuvant radiation prior to surgery, which has shown promise.

For patients with extra-abdominal tumors as well as those with recurrence despite local therapy, systemic medical therapy is often prescribed. Options include tamoxifen, which is thought to suppress desmoid growth due to the presence of estrogen receptor beta on tumor cells, particularly extra-abdominal desmoids. Similarly, nonsteroidal anti-inflammatory drugs (NSAIDs) such as sulindac, alone or with tamoxifen, have shown promising response rates. With either anti-estrogen or NSAID therapy, tumor shrinkage is often slow and delayed by many months.¹³

Finally, in patients who do not respond to non-cytotoxic therapy, trials have shown good response to treatment with either doxorubicin-based regimens or methotrexate with vinca alkaloids.¹⁴

Post-treatment surveillance includes clinical examination and radiographic assessment every 6 months for at least 3 years and then yearly thereafter.

Summary

This case report highlights the incidence of desmoid tumors, a rare but clinically significant cause of neoplastic disease. Although desmoids are uncommon, the asymptomatic nature of their progression and their locally invasive and aggressive behavior require clinicians to be aware of them, as they can cause significant functional impairment as well as morbidity and mortality if vital structures are involved. Surgical resection is the preferred therapy, though recurrence is high despite complete resection. Radiation therapy, as well as medical therapy with noncytotoxic and cytotoxic agents, has a role as an alternative to surgical therapy or experimentally in the neoadjuvant setting. Close follow-up of these patients is warranted, given the high rate of recurrence.

References

- Schlemmer M. Desmoid tumors and deep fibromatoses. *Hematol Oncol Clin North Am.* 2005;19:565-571.
- Li C, Bapat B, Alman BA. Adenomatous polyposis coli gene mutation alters proliferation through its beta-catenin-regulatory function in aggressive fibromatosis (desmoid tumor). *Am J Pathol.* 1998;153:709-714.
- Tejpar S, Noller F, Li C, et al. Predominance of beta-catenin mutations and beta-catenin dysregulation in sporadic aggressive fibromatosis (desmoid tumor). *Oncogene.* 1999;18:6615-6620.
- Hizawa K, Iida M, Mibu R, Aoyagi K, Yao T, Fujishima M. Desmoid tumors in familial adenomatous polyposis/Gardner's syndrome. *J Clin Gastroenterol.* 1997;25:334-337.
- Cheon SS, Cheah AY, Turley S, et al. Beta-catenin stabilization dysregulates mesenchymal cell proliferation, motility, and invasiveness and causes aggressive fibromatosis and hyperplastic cutaneous wounds. *Proc Natl Acad Sci U S A.* 2002;99:6973-6978.
- Way JC, Culham BA. Desmoid tumour. The risk of recurrent or new disease with subsequent pregnancy: a case report. *Can J Surg.* 1999;42:51-54.
- Shields CJ, Winter DC, Kirwan WO, Redmond HP. Desmoid tumours. *Eur J Surg Oncol.* 2001;27:701-706.
- Easter DW, Halasz NA. Recent trends in the management of desmoid tumors. Summary of 19 cases and review of the literature. *Ann Surg.* 1989;210:765-769.
- Carlson JW, Fletcher CD. Immunohistochemistry for beta-catenin in the differential diagnosis of spindle cell lesions: analysis of a series and review of the literature. *Histopathology.* 2007;51:509-514.
- Smith AJ, Lewis JJ, Merchant NB, Leung DH, Woodruff JM, Brennan MF. Surgical management of intra-abdominal desmoid tumours. *Br J Surg.* 2000;87:608-613.
- Melis M, Zager JS, Sondak VK. Multimodality management of desmoid tumors: how important is a negative surgical margin? *J Surg Oncol.* 2008;98:594-602.
- Nuytens JJ, Rust PE, Thomas CR Jr, Turriss AT 3rd. Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: a comparative review of 22 articles. *Cancer.* 2000;88:1517-1523.
- Janinis J, Patriki M, Vini L, Aravantinos G, Whelan JS. The pharmacological treatment of aggressive fibromatosis: a systematic review. *Ann Oncol.* 2003;14:181-190.
- Patel SR, Benjamin RS. Desmoid tumors respond to chemotherapy: defying the dogma in oncology. *J Clin Oncol.* 2006;24:11-12.

Review

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Desmoid disease in the context of familial adenomatous polyposis (FAP) consists of a spectrum of lesions, ranging from 3-dimensional tumors to 2-dimensional plaques. Even these plaques can cause symptoms, as they are commonly found in the retroperitoneum or small-bowel mesentery, where they pucker and distort tissues, leading to bowel and ureteric obstruction or ischemia. In the case reported by Venkat and associates,¹ a desmoid tumor distorted the colon of their patient and caused obstruction. Studies have shown that 30% of FAP patients will develop desmoid disease, with intra-abdominal desmoids comprising approximately 50% of cases and abdominal wall desmoids comprising 45% of cases.² Sporadic intra-abdominal desmoid tumors are rare, and in patients such as the one presented by Venkat and associates, FAP must be excluded.¹

Excluding Familial Adenomatous Polyposis

Desmoid disease in FAP is associated with 3' mutations in the adenomatous polyposis coli (*APC*) gene, though the genotype/phenotype correlation is neither universal nor exact. Risk factors for desmoid disease in FAP include female gender, a family history of desmoid disease, the presence of extracolonic manifestations of a germline *APC* mutation, and the presence of a 3' *APC* mutation.³ A 3' *APC* mutation is also associated with increasingly attenuated polyposis; thus, patients carrying germline mutations at the extreme 3' end of *APC* may have desmoids but few colorectal adenomas.⁴ Therefore, when patients present with an apparently isolated intra-abdominal desmoid tumor, colonoscopy is mandatory. Even if no adenomas are seen, both esophagogastroduodenoscopy and genetic testing for an *APC* and *MYH* germline mutation are recommended.⁵ In patients without genetic or phenotypic evidence for FAP, colonoscopic surveillance every 5 years is recommended.

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Staging Abdominal Desmoids

The literature concerning abdominal desmoids is full of small series and isolated case reports that often combine FAP-associated cases with sporadic cases. This reporting makes comparison and aggregation of studies and cases difficult. My colleagues and I have developed a system of staging abdominal desmoid disease that makes treatment planning more logical and potentially facilitates analysis of outcomes.⁶ Stage I tumors are small (<10 cm), asymptomatic, and stable. Stage II tumors are also small (<10 cm) but cause moderate symptoms (eg, pain or nausea) and are slowly growing. Stage III tumors are 10–20 cm in diameter and cause severe symptoms (eg, bowel or ureteric obstruction), whereas stage IV tumors are large (>20 cm), rapidly growing, or life threatening (eg, sepsis, fistula, necrosis with hemorrhage). The case presented by Venkat and associates¹ fits stage II. In our experience, the most severely symptomatic desmoid tumors are found in young women with FAP.⁷

Treating Desmoid Tumors

Medical Therapy

There is no predictably effective medical treatment for desmoid disease. The most commonly used options have been discussed in the case report by Venkat and associates¹ and include nonsteroidal anti-inflammatory drugs (NSAIDs; particularly sulindac 150–200 mg bid), estrogen-blocking drugs (tamoxifen up to 120 mg daily; raloxifene 120 mg daily), chemotherapy (methotrexate and vinorelbine, doxorubicin), and imatinib (Gleevec, Novartis).¹ Physicians tend to treat these patients according to the stage of their disease. Patients with stage I disease receive sulindac or no treatment. Patients with stage II disease are treated with sulindac and raloxifene, stage III disease with methotrexate and vinorelbine, and stage IV disease with doxorubicin (most recently, liposomal doxorubicin or doxorubicin hydrochloride [Doxil, Ortho Biotech]).^{6,8} The endpoint of treatment is not tumor disappearance but, rather, tumor stabilization and disappearance of symptoms.

Surgery

Surgery is the preferred treatment for abdominal wall desmoid tumors in FAP, as a margin-free resection (R0) is almost always possible. Recurrence rates are high, but morbidity is low.^{9,10}

Most intra-abdominal desmoids related to FAP are found in the root of the small-bowel mesentery, where they surround the superior mesenteric artery, making them unresectable (unless extensive enterectomy is contemplated).¹¹ In the case presented by Venkat and associ-

ates, as with some FAP-associated desmoids, the tumor is more distal in the mesentery.¹ This, plus the location in the mesocolon, allows for the possibility of resection. If an obstructing desmoid is unresectable, other surgical options include bypass or diversion. The risk of recurrence after desmoid excision ranges from 50% to 80%⁹⁻¹¹; thus, surgery should be followed by prophylactic sulindac.

Resectability of intra-abdominal desmoid tumors can be determined by clinical examination (mobility of the mass) and by CT scan. Symptomatic intra-abdominal desmoids should be resected if possible.

Radiation

Desmoid tumors are sensitive to radiation, which is often used for extra-abdominal tumors. For intra-abdominal lesions, the proximity of the intestine makes radiation therapy a dangerous choice and generally a last resort.

Natural History of Desmoid Disease

Two of the challenges posed by desmoid disease are its unpredictability and its clinical heterogeneity. It is difficult to predict the clinical course of desmoid disease in any particular patient. However, in the context of FAP, it has been found that desmoids behave the worst in young nulliparous women⁷ and that pregnancy ameliorates symptoms.¹² In over 100 FAP patients with desmoid disease, 10% experienced complete regression of their tumor and 7% died from aggressive, unresponsive disease; the remaining 83% experienced variable growth and were never desmoid-free, though they were not severely affected.⁷ The patient treated by Venkat and associates¹ was a 46-year-old woman, who might thus have been expected to have a relatively benign course of desmoid disease. Her birth history would have been helpful in further defining the likelihood of symptomatic recurrence. Finally, there was no mention of the presence of plaque-like lesions elsewhere in the mesentery of the bowel during laparotomy.

Summary

An intra-abdominal desmoid tumor has a typical appearance on computed tomography scan and, in the absence of FAP, should be biopsied to exclude low-grade sarcoma

or tumors of other histologies. Treatment is based upon resectability and symptomatology. Symptomatic resectable lesions should be removed, whereas asymptomatic lesions may be observed. Nonresectable tumors are treated with NSAIDs, estrogen blockers, or chemotherapy, depending upon the stage of the tumor and the response to therapy. The patient treated by Venkat and associates¹ should undergo esophagogastroduodenoscopy, colonoscopy, and testing for a germline mutation in *APC*. Abdominal magnetic resonance scan or computed tomography scan should be performed in 6 months, but, thereafter, the interval may be extended, as long as the patient is asymptomatic and previous scans show no recurrence. If *APC* testing is negative for mutations, and all other tests are normal, colonoscopy every 5 years is reasonable.

References

1. Venkat D, Levine E, Wise WE Jr. Abdominal pain and colonic obstruction from an intra-abdominal desmoid tumor. *Gastroenterol Hepatol (N Y)*. 2010;6:662-665.
2. Hartley JE, Church JM, Gupta S, McGannon E, Fazio VW. Significance of incidental desmoids identified during surgery for familial adenomatous polyposis. *Dis Colon Rectum*. 2004;47:334-338; discussion 339-340.
3. Elayi E, Manilich E, Church J. Polishing the crystal ball: knowing genotype improves ability to predict desmoid disease in patients with familial adenomatous polyposis. *Dis Colon Rectum*. 2009;52:1762-1766.
4. Gardner RJ, Kool D, Edkins E, et al. The clinical correlates of a 3' truncating mutation (codons 1982-1983) in the adenomatous polyposis coli gene. *Gastroenterology*. 1997;113:326-331.
5. Benoit L, Faivre L, Cheynel N, et al. 3' Mutation of the APC gene and family history of FAP in a patient with apparently sporadic desmoid tumors. *J Clin Gastroenterol*. 2007;41:297-300.
6. Church J, Lynch C, Neary P, LaGuardia L, Elayi E. A desmoid tumor-staging system separates patients with intra-abdominal, familial adenomatous polyposis-associated desmoid disease by behavior and prognosis. *Dis Colon Rectum*. 2008;51:897-901.
7. Church JM. Desmoid tumors in patients with familial adenomatous polyposis. *Sem Colon Rectal Surg*. 1995;6.1:29-32.
8. Bertagnolli MM, Morgan JA, Fletcher CD, et al. Multimodality treatment of mesenteric desmoid tumours. *Eur J Cancer*. 2008;44:2404-2410.
9. Clark SK, Neale KF, Landgrebe JC, Phillips RK. Desmoid tumors complicating familial adenomatous polyposis. *Br J Surg*. 1999;86:1185-1189.
10. Latchford AR, Sturt NJ, Neale K, Rogers PA, Phillips RK. A 10-year review of surgery for desmoid disease associated with familial adenomatous polyposis. *Br J Surg*. 2006;93:1258-1264.
11. Smith AJ, Lewis JJ, Merchant NB, Leung DH, Woodruff JM, Brennan MF. Surgical management of intra-abdominal desmoid tumors. *Br J Surg*. 2000;87:608-613.
12. Church JM, McGannon E. Prior pregnancy ameliorates the course of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis. *Dis Colon Rectum*. 2000;43:445-450.