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NARRATIVE REVIEW

A Review of the Clinical Presentation, Outcomes, and Treatments of Patients Having Desmoid Tumors

Carlos Figueredo[1,*] and Thomas Schiano[2,†]

[1]Department of Gastroenterology and Hepatology, Montefiore Medical Center/Albert Einstein College of Medicine, New York, New York; and [2]Recanati-Miller Transplantation Institute, The Mount Sinai Medical Center, New York, New York

Desmoid tumors (DTs) are deep fibroblastic neoplasms that arise from musculo-aponeurotic stromal elements. DTs may result in significant morbidity by infiltrating vital anatomic structures. Their mortality is often due to the local aggressiveness, most commonly when intra-abdominal in location. Some indolent DTs can be observed expectantly; infiltrative tumors require an aggressive and multidisciplinary approach and are offered conservative therapies such as nonsteroidal anti-inflammatory drugs or antiestrogens when surgery is not feasible. Comparably, chemotherapy is considered for those cases not amenable to surgery or radiation. Bowel resection and at times intestinal transplantation may be necessary. However, DTs may recur postsurgery making long-term management of these patients. Herein, we review the genetics, clinical presentations, outcomes, and treatments of DTs.

Keywords: Abdominal Pain; Familial Adenomatous Polyposis; Gardner's Syndrome; Intestinal Transplantation

Introduction

Desmoid tumors (DTs) are fibrous tissue tumors that emerge from the musculo-aponeurotic structures with potential to grow in any location of the body. They are uncommon, comprising approximately 3% of all soft-tissue tumors and 0.03% of all neoplasms. DTs can be divided based on their etiology into 2 groups: sporadic and familial such as in familial adenomatous polyposis (FAP) and Gardner's syndrome. Another classification can further divide DTs as per their location into 3 groups: extra-abdominal, intra-abdominal, and multiple. The incidence of familial DTs is seen in up to 25% of patients with FAP.[1]

Epidemiology

The incidence of DTs is approximately 2%–4% per million people. Sporadic DTs have been reported to be more common in women with some clinical trials demonstrating a 2:1 vs a 4:1 gender ratio when presenting in the third to fourth decade of life. The overall intra-abdominal DTs sex ratio tends to be equal.[2] The mean age of presentation is 40 years, but familial cases can be seen in younger individuals. There is no reported race or ethnicity predilection. DTs are widely known for their slow growth and high recurrence rates, which can be up to 87%. They can impact the patient's quality of life by their local aggressive nature and anatomical disruption of vital organs with a high tendency to recur despite radical medical or surgical management.[3–5]

Familial DTs have an approximate 800- to 1000-fold higher incidence of developing DTs. FAP is more frequently associated with abdominal DTs, especially the Gardner's variant. Five to thirty percent of DTs are found in the mesentery in FAP patients. Conversely, approximately 10% of patients with DTs have or will develop FAP. DTs represent the most common cause of death in those FAP patients undergoing prophylactic colectomy.[2]

Genetics

Familial-related cases (FAP, Gardner's syndrome) are autosomal-inherited. These syndromes are caused by a mutation in the adenomatosis polyposis coli (APC) gene; most mutations are located on chromosome 5q21 but one-third of these cases are related to a spontaneous gene mutation rather than familial related.[4,5] Mutations on CTNNB1 have been linked to sporadic DTs; mutations for beta-catenin are found in 85% of cases of sporadic DTs.

Wnt/B-Catenin Pathway

Alterations in the Wnt/B-catenin pathway have been associated with both FAP and sporadic DTs. Wnt protein plays an important role in the proliferation of mesenchymal cells. Mutations in this pathway result in the absence of the Wnt protein and dysregulation of fibroblast proliferation,

*Author. †Co-author.

Abbreviations used in this paper: **APC, adenomatosis polyposis coli; COX-2, cycloocygenase 2; CT, computerized tomography; DT, desmoid tumors; FAP, familial adenomatous polyposis; FDG, fluorodeoxyglucose; IF-1, interferon type-1; MRI, magnetic resonance imaging; PDGF, platelet-derived growth factor; US, ultrasonography.**

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keeping mesenchymal stem cells undifferentiated (proliferative state). B-catenin is bound to a complex of different protein kinases such as CK1γ and GSK-3β. Normally, this complex oversees phosphorylation, ubiquitination, and degradation of B-catenin in the proteasome. When a mutation occurs, this complex cannot be formed. As a result, beta-catenin is not degraded and accumulates before translocating to the nucleus. Its accumulation activates T-cell factor, which in turn causes transcription of target genes. One of those genes includes cyclooxygenase 2 (COX-2), which has been reported to contribute to tumorigenesis by apoptosis inhibition, angiogenesis stimulation, and cell proliferation modulation through increased expression of growth factors such as platelet-derived growth factor (PDGF). Comparably, Interferon type-1 (IF-1) is involved in the biogenesis of DT, possibly by modulating mesenchymal progenitors and aiding in their proliferation.[6]

APC Mutation

Mutations in the APC gene germline create an APC protein truncation and deprivation of the B-catenin regulatory domain, resulting in an increased level of nonphosphorylated protein. Consequently, nonphosphorylated B-catenin translocate to the nucleus, activating the transcription of genes such as CYCD1 and MYC, promoting their proliferation and resulting in their accumulation in the nucleus.

APC bi-allelic mutations have been linked with familial DTs. In FAP, a mutated germline on one allele is inherited. In this setting, one somatic mutation is required in the opposite allele for the tumor to grow. In contrast, patients with a normal germline, somatic mutations in both APC alleles are required for familial DTs to develop. Mutations result in one change of the distal to the second beta-catenin binding/degradation repeat of the gene 3′ to codon 1399. A study identified that patients with the C3 genotype (APC mutation in codons 1395–1493) have up to a 100% risk for developing DTs.[7]

CTNB1 Mutation

The CTNNB1 gene (exon 3) also plays an important role in the phosphorylation of beta-catenin. Multiple mutations have been related to the development of DTs; data suggest that S45F mutations are associated with a higher rate of recurrence after surgical resection of a primary desmoid tumor.

Lazar et al found that 23% of patients with a 45F mutation were free from progression at 5 years of follow-up, whereas 59% of patients with a 41A mutation were stable. In another study, patients with DTs and a nonmutated CTNNB1 gene had fewer recurrences.[8,9]

Classification

DTs can be classified as abdominal and extra-abdominal. Extra-abdominal DTs are most commonly observed in the areas of the shoulder and pelvic girdle, chest wall, and neck. The abdominal subtype can be further classified as superficial (abdominal wall), and intra-abdominal, both of which are histologically similar. Intra-abdominal DT can occur in any location of the abdominal cavity. Pregnancy and local trauma such as prior surgery have been associated with their development.[10]

DTs can be further divided based on their origin into sporadic (idiopathic) and familial forms (FAP or Gardner). Often, the sporadic subtype is found extra-abdominally, whereas the familial type tends to have greater intra-abdominal involvement. DTs can be multifocal and multicentric. Despite the esthetic concerns and local pain that abdominal wall DTs cause, they are typically less invasive and have less morbidity than intra-abdominal tumors. Deep or intra-abdominal DTs can be localized to the mesentery, pelvis (representing up to 70% of cases), or retroperitoneum. FAP has been associated with 85% of cases of mesenteric intra-abdominal DTs. Sporadic DTs tend to be extra-abdominal when compared to familial related DTs.[11]

Clinical Presentation

The natural history of DTs is difficult to predict. In most instances, these lesions are identified incidentally on imaging studies performed for another indication but they more commonly present with slow growth and are often diagnosed at advanced stage after they have caused local infiltrative and destructive effects proportional to their size and location. Therefore, symptomatology correlates to the affected area with potential intestinal, vascular, neurologic, or genitourinary obstruction. Manifestations include related pain, functional impairment, bowel obstruction, and in some cases, perforation necessitating large sections of bowel resection. Based on the wide spectrum of complications that can arise from DT progression, they can be further divided based on the associated morbidity into nonlife threatening (bowel obstruction, fistula formation, ureteral obstruction, and hydronephrosis) and life threatening (hemorrhage, sepsis, bowel perforation, and peritonitis).[11]

In some instances, spontaneous regression of DTs has been observed. In one study, 10% of DTs resolved spontaneously. In contrast, 50% remain stable after diagnosis and 10% may have rapid progression. Spontaneous regression has been reported mostly in postmenopausal women or in women undergoing oophorectomy, which further supports the relationship between DTs and estrogens.[12]

Diagnosis

Diagnosis relies on a detailed history to identify factors associated with DTs. High levels of estrogen related to either physiologic states (pregnancy) or acquired (oral contraceptives, estrogen agonists) may help explain the female preponderance in this disease. At the same time, DT cases have been reported to regress after menopause or with the use of

antiestrogen therapies such as tamoxifen.[10] FAP-related DTs have been correlated with a previous history of prophylactic procto-colectomy. Prophylactic proctocolectomy with an ileoanal reservoir is a well-established procedure in the prevention of colorectal neoplasia. It is thought that predisposed mesenchymal cells in these patients infiltrate the mesentery provoking wrinkling of the bowel margin and overgrowing regional trauma unintentionally generated because of the procedure. Three-year postsurgery follow-up screening is often recommended for patients with known familial-related syndromes who underwent intra-abdominal surgery. The differential diagnosis of extra-abdominal desmoid tumors includes other neoplasm such as lymphoma, sarcoma, and fibrosarcoma. Imaging characteristics are not pathognomonic, therefore making histopathological analysis necessary for definitive treatment.[7]

History and Physical

The diagnosis of sporadic DTs is based on detailed history and physical, patient symptomatology and radiologic testing, history of recent trauma (in view of the post-procedure release of growth factors during the initial phase of wound healing can potentially transmit signals that reinforce the activation of β-catenin) or intra-abdominal surgery might help suggest the etiology of the lesions in 25% of cases, often presenting an average of 3 years to any time postprocedure . Familial-related DTs such as in FAP and Gardner syndrome have been described with colonic adenomatous polyps (tubular, villous, tubule-villous), gastric and small intestinal adenomatous polyps, and risk of periampullary carcinomas. In addition, osteomas have been seen in 50% of cases and multiple types of skin lesions (fibromas, neurofibromas, pigmented skin lesions) that occur in nearly two-third of the affected population. Malignant transformation potential has been documented in both the thyroid (papillary thyroid cancer) and the liver. Genetic testing and genetic surveillance of first-degree relatives is useful and recommended for familial-related DTs.[6,7]

Intra-abdominal sporadic DTs are often retroperitoneal and, in the pelvis, whereas intra-abdominal mesenteric DTs are more commonly associated with Gardner's syndrome. Mesenteric DTs are quite uncommon. Sporadic tumors tend to be larger in size with a solitary lesion as compared to Gardner's syndrome which often presents with multiple mesenteric lesions which are smaller in size. Family history is a helpful piece of information when assessing risk factors in DTs. Patients with a strong family history (defined as more than 30% of affected family members with DTs) should be recommended to undergo genetic testing.[10]

Histopathological Analysis

Grossly, DTs are seen as firm, irregular, rubbery, gray-white soft-tissue masses with elongation in the direction of muscle fibers that resemble a fibrotic scar tissue. They tend to infiltrate muscle fibers as opposed to a fibroma which is encapsulated. A cross-sectional aspect of the DT reveals a glistening white, coarsely trabeculated surface resembling scar tissue.[1]

The size of DTs is relevant as a prognostic factor and to assess the response to treatment. They can vary from 5–20 cm in diameter. Intra-abdominal desmoid tumors commonly present in 2 forms; large firm to palpation masses or as sheet-like white plaques found within the mesentery which has been previously described in some literature as the incipient form of the DT. Both can also infiltrate surrounding tissues, potentially causing dissection of inter-loop adhesions and in extreme cases even contributing to small bowel obstruction.[1]

Histological analysis reveals a poorly circumscribed tumor lacking a true capsule. DTs are predominantly composed of collagen which surrounds poorly circumscribed bundles of elongated, slender, spindle-shaped cells of uniform appearance. Cell-to-cell contact is minimal due to the abundant amount of collagen around neoplastic cells. The previously aforementioned dense bundles of spindle cells contain regular small and sharply defined nuclei with pale cytoplasm, negative for mitoses or giant cells. Usually, one to 3 small nucleoli are commonly seen. The cellularity can vary within the same lesion. In some instances, telomerase length and activity are normal which is a sign that these lesions are histologically benign. On the other hand, some DTs are described as aggressive fibromatosis when marked cellularity is observed which reflects the aggressive local behavior. Macrophages, giant cells, and lymphocytes are present peripherally. Often, fragments of muscle cells can be identified embedded within the tumor. Histological features such as hyperchromatasia and atypia are absent. Myofibroblasts appear similar occurring during the proliferative stage of wound healing. Large amounts of myxoid stroma may be seen in some DTs, especially those occurring in the mesentery (Figure 1). Immunohistochemistry analysis is positive for multiple muscle cell markers such as vimentin, alpha smooth muscle active, and muscle actin. DTs also stain positive for B-catenin, cyclooxygenase 2, tyrosine kinase PDGFRβ, androgen receptor, and estrogen receptor beta but are negative for desmin, S-100, h-caldesmon (h-CD), CD34, and c-KIT.[1,13]

Incisional biopsy is often preferred over fine needle aspiration in terms of biopsy sampling to better differentiate between DTs and other tumors. Biopsy does not seem to increase the risk for further growth or seeding of the tumor. Histological analysis alone is not pathognomonic for diagnosis and correlation in right clinical setting is necessary[13] (Figure 2).

Imaging

The role of imaging in diagnosing DTs diagnosis relies most on the assessment of the extension, staging, and burden of the lesions. Ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI) are used for staging. On US, DTs can present as well or poorly defined hypoechoic soft-tissue masses with variable vascularity. DTs can have variable

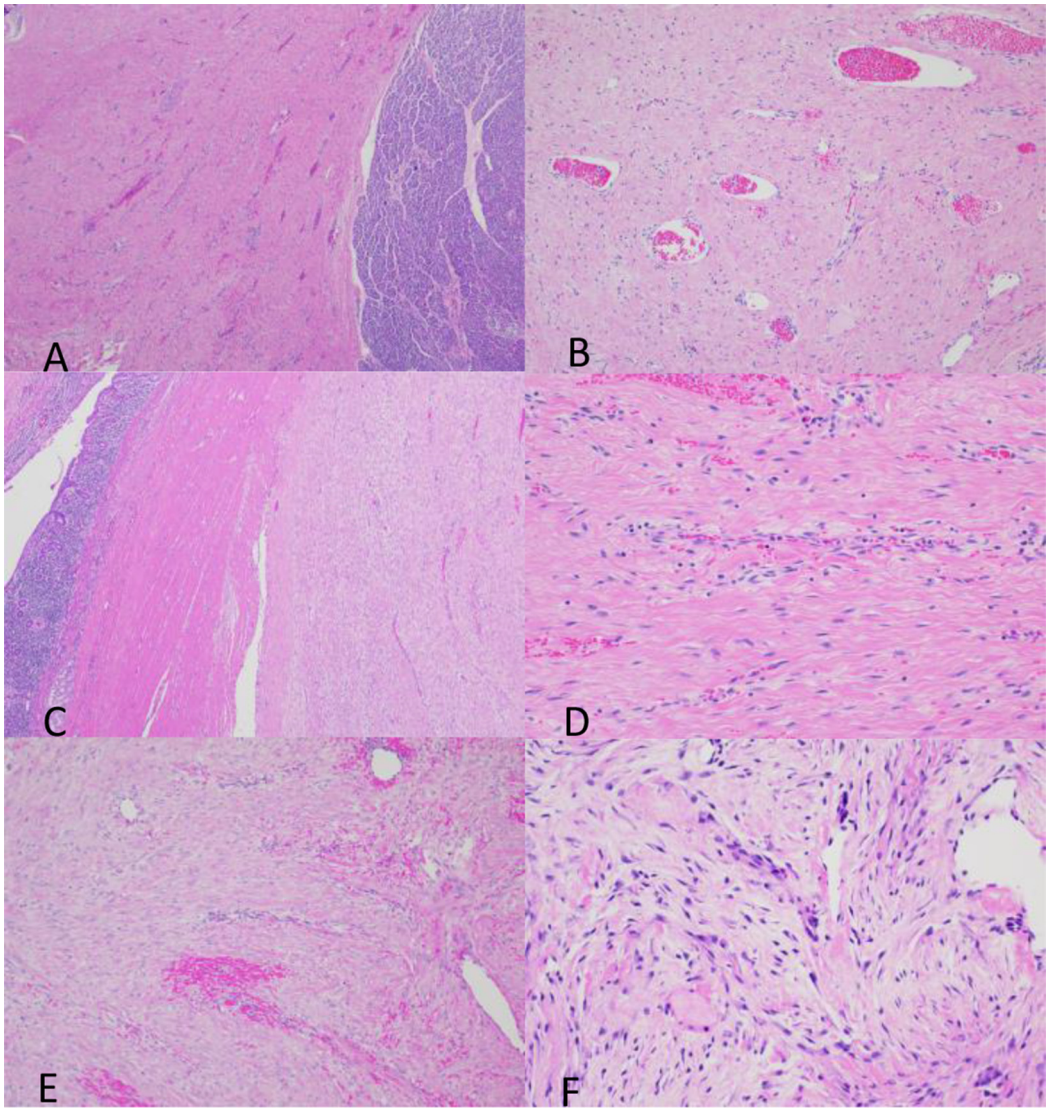

Figure 1. A myofibroblastic neoplasm adherent to pancreatic tissue which does not distort the pancreatic lobulo-acinar architecture. The bland proliferation of myofibroblastic cells is interspersed with small to medium-sized dilated stromal blood vessels (A). The stromal vasculature of intra-abdominal desmoid-type fibromatosis may feature vascular ectasia with dilated and congested blood vessels with perivascular hyalinization (B). An intra-abdominal desmoid tumor adherent to the serosal side of a segment of small intestine revealing a bland proliferation of myofibroblastic cells interspersed with compressed stromal blood vessels (C). Classically, desmoid-type fibromatosis features a fascicular architecture with long fascicles of spindled cells in a collagenous stroma. The characteristic stromal vasculature of this tumor includes elongated and compressed blood vessels between fascicles of neoplastic myofibroblasts (D). Stromal microhemorrhages or extravasated red blood cells are a variable finding in this tumor (E). A storiform growth pattern is commonly seen in desmoid-type fibromatosis revealing spindled to stellate neoplastic cells with bland cytology and small vesicular nuclei (F). [Original magnifications 4× (A), 10× (B) 4× (C), 20× (D), 10× (E), 20× (F)].

echogenicity depending upon the amount of collagen, fibrosis, and cellular components within the lesion. Studies have shown the presence of stellar-type configuration with multiple irregular sunburst-like extensions along fascial planes which can support the diagnosis of extra-abdominal DTs.[14]

In contrast, CT scans are extremely helpful in diagnosing intra-abdominal lesions. The myxoid stroma is detected as hypodense, while collagenous and fibrotic components are seen as isodense or hyperdense tissue.[14] Comparably, CT scans may have variable attenuation as in US, depending upon the amount of collagenous and myxoid contents. DTs show avidity following intravenous contrast administration. However, the degree of enhancement depends on varying myxoid and collagenous components within the tumor. Necrosis is frequently absent.[14,15] CT scan provides essential information in regard to treatment planning, anatomical relationship of the tumor with surrounding vessels and organs, and detecting complications such as bowel obstruction, ischemia, and hydronephrosis that can be seen (Figure 3).

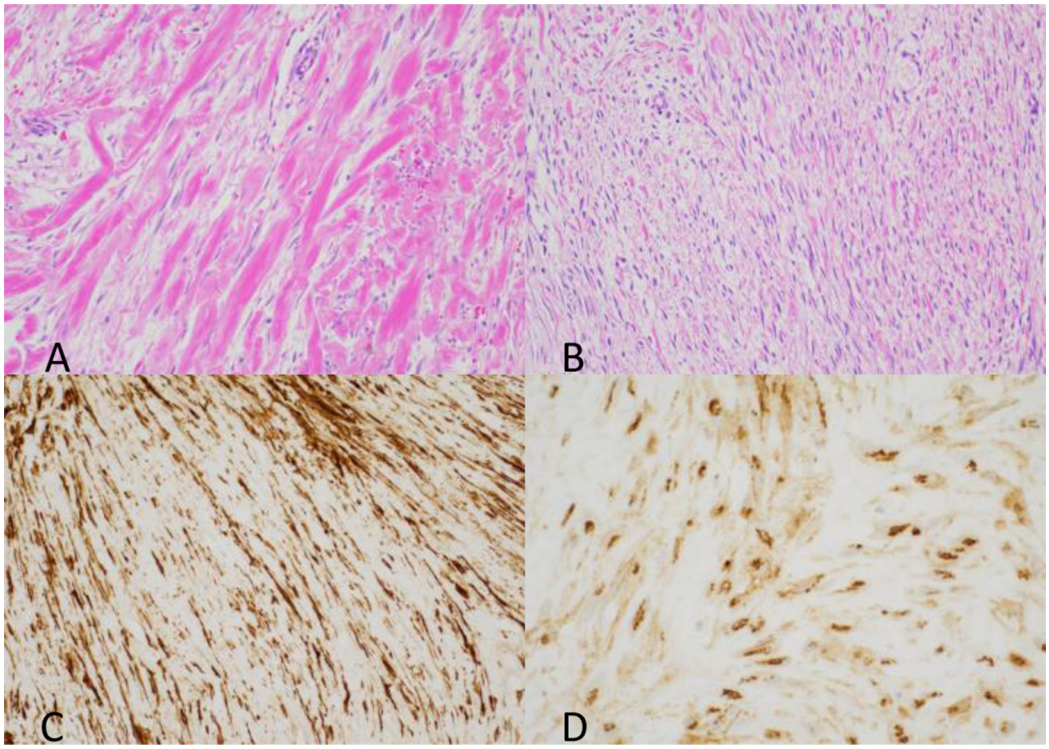

Figure 2. Intra-abdominal and mesenteric desmoid tumors occasionally display keloidal collagen composed of thick and glassy bundles of collagen (A), and myxoid or edematous stromal change (B). Smooth Muscle Actin (SMA) immunohistochemical stain positivity is common in desmoid-type fibromatosis with fine cytoplasmic expression (C). β-catenin immunohistochemical stain positivity with nuclear expression is seen in more than 70% of cases, corresponding to abnormal nuclear localization of β-catenin (D). [original magnifications 20× (A), 20× (B), 20× (C), 40× (D)].

MRI with gadolinium demonstrates mild to moderate enhancement in delayed phase postcontrast enhanced images. MRI is often demonstrating low signal intensity on T2 weighted sequences. However, some cases have prominent cellular stroma and myxoid matrix can manifest as heterogeneous T2 hyperintense areas. Nonenhancing T1 and T2 hypointense bands, also known as the "band sign" can be seen in 60%–90% of DTs, but it is not pathognomonic as it can be present in other musculoskeletal soft-tissue tumors.[16] No features can distinguish between sporadic and familial DT. As a result, MRI is considered the imaging modality of choice, superior to CT scan to assess extension, and involvement of adjacent structures and possibly to prognosticate resectability. The role of fluorodeoxyglucose (FDG) positron emission tomography-CT scan has not been fully studied; DTs tend to have mild FDG avidity. FDG positron emission tomography-CT however may be useful in monitoring efficacy of systemic therapy as reduction in FDG uptake has been correlated with decrease in tumor mitosis in DTs[15–17] (Figure 4).

Staging

There is a staging system established by Collaborative Group of the Americas on Inherited Colorectal Cancer in 2005 based on tumor size, symptoms, growth, and presence of complications. Based on this staging process when multiple DTs are present, the larger tumor with the highest stage is used. Each tumor has an assigned stage (I through IV) and associated mortality (Table). Staging will be assigned regardless of the possibility of improvement post-treatment.[12]

Imaging is crucial in the staging and feasibility of different therapeutic options. Conventionally, size is a relevant feature in DTs which allows to estimate prognosis and dictates therapy response based on the tumor response criteria RECIST 1.1. However, this criterion can often underestimate the effect therapy, especially when systemic targeted therapies are used.[12]

Differential Diagnosis

Mesenteric DTs commonly present in patients with a known history of FAP in whom colorectal cancer may result in mesenteric metastases, mimicking DTs. However, some patients do not have a history of FAP. In such circumstances, the presentation can potentially be confused with other rare entities, such as carcinoid tumor and sclerosing mesenteritis which can mimic primary mesenteric neoplasms, making the diagnosis of DTs at times difficult. Carcinoid tumors arise from the small bowel and lymphatically can spread to the mesentery are then seen as small tumors on CT scan mesenteric panniculitis can show areas of focal increased

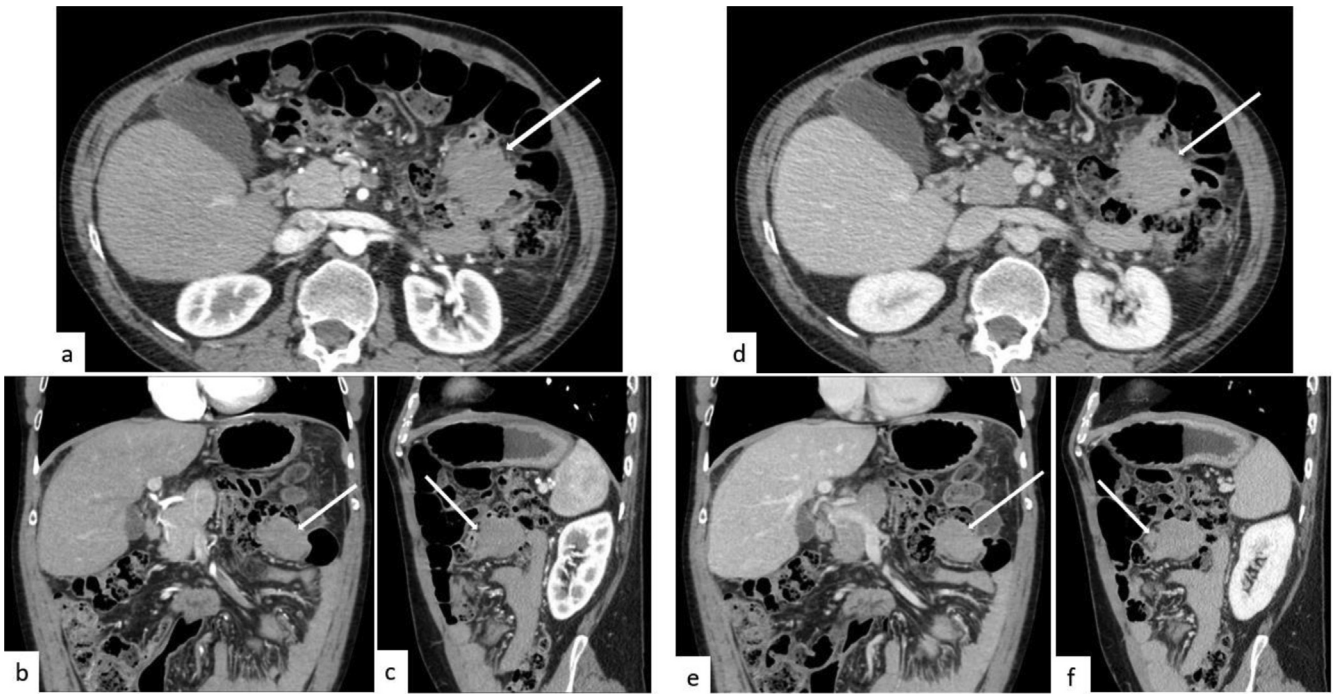

Figure 3. Incidental mass on screening CT abdomen/pelvis with IV contrast. Axial, coronal, and sagittal images in arterial (A–C) and venous phase (D–F) show a 4.5 cm homogenous, moderately enhancing mesenteric mass in the left abdomen contiguous with the small and large bowel (white arrow). Exploratory laparotomy was performed, and the mass was excised. Pathology confirmed a desmoid tumor, with fibromatosis extending into the muscularis propria of the small intestine.

attenuation within the mesenteric fat and CT scan, a pattern known as "mystic mesentery". In view of its rarity and the difficulty to distinguish these disease entities by CT scan alone, histopathological analysis is an essential tool in making the final diagnosis. In addition, other primary mesenteric tumors of mesenchymal origin are lipomas, schwannomas, smooth muscle, and sarcomas, should also be ruled out. A CT-guided fine-needle aspiration biopsy helps in differentiating DTs from other neoplasms (lymphoma, gastrointestinal stromal tumor, mesenteric metastases, pleomorphic sarcoma, fibrosarcoma, giant cell tumor of the tendon sheath) when imaging features are not conclusive.[18–21]

Treatment

Conservative Management

Management of DTs represents an ongoing challenge for both the physician and patient in view of the unpredictable tumor behavior, significant morbidity, and high rate of recurrence. Rarely DTs regress spontaneously (pregnancy, cessation of exogenous estrogen, menopause), accounting for 20–30 of the cases. Also, 50%–60% of DTs do not grow after the diagnosis. Asymptomatic DTs are not treated and close monitoring with no further intervention is recommended except for annual clinical and or radiological (CT scan, MRI) surveillance within 1–2 months and then at 3–6 months intervals after proper diagnosis is established (biopsy, imaging).

Tumors having a slow growing behavior but symptomatic (stage I and II) in a location distal to critical structures (mesenteric, head, and neck) are best managed conservatively after proven subsequent progression and symptom burden on at least 3 ongoing assessments. In these cases, pain control and quality of life are 2 main priorities of the conservative management. Multiple factors such as younger age, having mesenteric and extremity DTs, and larger tumor size have been associated with higher rates of progression, which may convey a higher morbidity. Comparably, FAP-associated DTs have a higher rate of 44% recurrence. The specific therapy should be guided as per the anatomic site and it is recommended to have the patient involved in the decision-making process in a stepwise approach with an experienced multidisciplinary team of doctors including surgeons, gastrointestinal oncologists, and healthcare centers with access to intestinal transplant programs.[21]

Medical Therapy

Sporadic DTs are one of the first entities that showed a clinical response to nonsteroidal anti-inflammatory drugs (NSAIDs) dating back to the 1980s. NSAIDs provide stabilization of B-catenin through its independent antitumor activities on COX-2 and induce remission of B-catenin activity of malignant cell lines, provoking cell cytoreduction and degradation, thus avoiding the development of new DTs and inhibiting the growth of existent lesions with a durable effect. However, most trials have only shown short-term efficacy. Therefore, NSAIDs such as sulindac, meloxicam, celecoxib, and indomethacin are the agents of choice with proven effectiveness. Data supporting the efficacy in FAP-

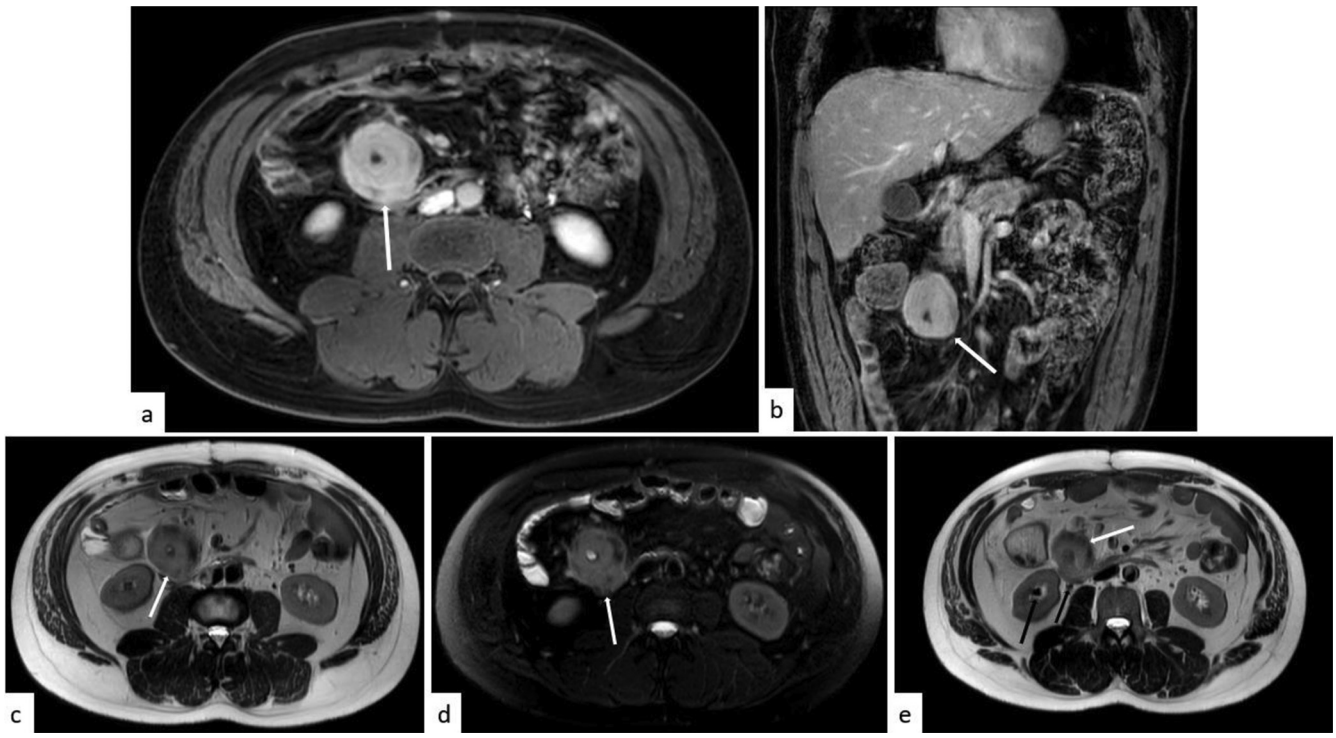

Figure 4. MRI with and without contrast demonstrate mass measuring 5.2 cm in greatest dimension (white arrow). The mass again demonstrates mild enhancement on post-contrast T1 weighted sequences (A, axial; B, coronal) and hypointensity on T2 weighted sequences (C). There is mild hyperintensity on T2 fat saturated sequence (D). The mass now impinges on the right ureter, causing mild right hydroureteronephrosis (E, black arrows). The mass additionally abuts the small bowel and causes mild proximal dilatation. The decision was made to excise the mass; pathology revealed recurrent desmoid tumor.

associated DT patients are unknown. However, there is clearly some proven benefit for the chemo-preventative effects of NSAIDs on FAP-associated polyps.[22]

Hormonal Therapy

DTs have uniform expression of estrogen receptor beta which provides the mechanism for the action of anti-estrogenic compounds in the treatment of DTs. Among available agents, tamoxifen and toremifene have been the most widely studied. Tamoxifen is associated with a clinical benefit in about 30% of the cases, with most patients having a symptomatic benefit with no significant radiological changes. Both tamoxifen and toremifene have been shown to have antiproliferative actions in modulating transforming growth factor-B and its receptor. Other agents, including raloxifene either alone or in combination, have shown similar results. The main downside is their side effect profile (flushing, headache, bleeding, need for contraception, prothrombotic state) which make them a less preferred option for patients' long term.[22–25]

Chemotherapy

Full-dose chemotherapy is often used when a rapid response is desired (intra-abdominal DTs). In these cases, anthracycline-based regimens are used and have proven to have an approximate 50% response rate. Different anthracycline chemotherapeutic agents such as Dacarbazine (DTIC)–Doxorubicin (DOX) are proven to be effective and relatively safe. DTIC-DOX is the first-line treatment, but careful monitoring is required with possible titration down to minimal doses to avoid severe adverse effects. For patients who are unable to tolerate DTIC-DOX, imatinib mesylate (tyrosine-kinase inhibitor) has proven to exert local control in otherwise nonsalvage unresectable DTs by blocking platelet-derived growth factor receptor PDGFR α and PDGFR-β activation and has been reported to be effective in advanced disease. Other options such as pegylated liposomal doxorubicin have been reported to have significant activity with an acceptable toxicity profile (less cardiotoxicity).[26,27]

Other protocols support the use of low-dose chemotherapy based on methotrexate (MTX) and vinca alkaloid agents (vinblastine or vinorelbine), which are agents shown to delay the progression of the disease and avoid life-threatening tumor infiltration such as in unresectable mesenteric DTs. The benefit of this regimen lays in the less toxic, cumulative effect when compared to anthracyclines. Clinical and radiological benefits have been seen in more than 80% of patients regardless of the CTNNB1 mutation status. This combination has been associated with radiological responses in about 50% of involved patients, lasting more than 5 years.[28,29]

Table. Intraabdominal Desmoid Tumors Staging[12]

Stage	Symptoms	Size (diameter)	Growth	5-y survival
I	Asymptomatic[12]	<10 cm	Not growing	95%
II	Mildly symptomatic (sensation of mass, pain, no restriction)[12]	<10 cm	Not growing	100%
III	Moderately symptomatic (sensation of mass, pain, restrictive but not hospitalized)[12]	10–20 cm	Slowly growing	89%
IV	Severely symptomatic (sensation of mass, pain, restrictive, and hospitalized) ± septic complication such as fistula and abscess[12]	>20 cm	Rapidly growing	76%

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors target the inhibiting receptors of PDGFs and vascular endothelial growth factor which play a critical role in DT initiation and progression. Imatinib was the first tyrosine kinase inhibitor studied as a treatment in patients with progressive DT, with a disease response of 10%–15% and disease control of 40%–70% at 6 months. Lower PDGFR-B serum values were observed in responding patients. Imatinib has also been effective in patients bearing the S45F mutation of CTNNB1.[27] Sorafenib is a multitarget inhibitor of tyrosine-kinase receptors including vascular endothelial growth factor receptors and PDGFRs, and in a retrospective cohort, the response rate was 25% with disease stabilization rate of 70%. Furthermore, a phase III–randomized, placebo-controlled trial (ALLIANCA) of sorafenib (400 mg daily) showed progression-free survival was 81% in the treatment group with an objective response rate of 33%. A randomized phase II study (DESMOPAZ) is currently investigating pazopanib vs IV MTX/vinblastine in adult patients with progressive DT with initial results showing a 6-month disease control rate of 83.7% for the pazopanib group and 45% with MTX-vinblastine with objective response rates of 37% and 55%, respectively.[28]

Molecular Therapies

Two new investigational agents targeting β-catenin, tegatrabetan (BC-2059), and the gamma secretase inhibitor have shown promising outcomes via their direct stimulation of β-catenin degradation promoting the apoptosis of DT cells in the Notch pathway and downregulating the Wnt/APC/β-catenin pathway with subsequent degradation of DT cells, respectively.[30] The Wnt/B-catenin inhibitors are hypothesized to have a central role in the therapeutics of DTs. Teratrabetan directly and selectively interferes with the interaction between B-catenin and transducing B-like protein (TBL1/TBLR1) which inhibits B-catenin nuclear translocation and promotes its degradation. It has been shown to have molecular in vitro and in vivo activity. Currently, a phase I first-in-human trial is currently in the recruitment process of DT patients. Furthermore, gamma-secretase inhibitors (GSIs) were originally developed as anti-Alzheimer agents and have been repurposed as anticancer agents because of their anti-Notch activity. Nirogacestat had a significant activity against DTs in a phase I study, with only partial response to GSIs in the medical refractory DTs group. In both studies, Nirogacestat was well tolerated.[31]

During a preliminary phase I study, nirogacestat showed impressive activity against DTs with 5 of 7 patients experiencing partial response and the other 2 with stable disease progression, which supports the role of GSIs in the medical therapy of refractory DT. In a subsequent study of 16 patients, 29% of patients had a partial response for duration of more than 2 years while the other 29% had prolonged stable disease. Most importantly, Nirogacestat appears to have an excellent side-effect profile. A phase 3 trial comparing Nirogacestat with placebo is expected to confirm these early promising results.[31]

The Nirogacestat inhibition of the Notch signaling through the Notch intracytoplasmic domain cleavage blockade has been suggested as a potential therapeutic target in the genesis of DTs. Nirogacestat was previously evaluated in the treatment of leukemia. However, it also inhibits the Notch pathway in DTs by inhibiting Notch intracytoplasmic domain and Hes1 expression. The blockade of the Notch pathway contributes to the inhibition of DT cell growth. Similarly, treatment with it reduced DT growth through its effect on halting the apoptotic effects by inhibiting the Notch pathway.[32]

Similarly, Nirogacestat inhibition via gene expression studies has revealed that the known WNT/B-catenin target gene WISP2 is upregulated in tumors after treatment, suggesting that WISP2 may act as a tumor suppressor. Clinical trials investigating the role of WISP2 in the DT and nirogacestat response have shown that WISP2 can regulate integrin which reportedly induces the Notch and WNT pathways. Therefore, the overall antitumor effects are related to an overexpression of WISP2 and thereby enhancement of WNT/B-catenin pathway regulation.[32]

In addition, immune checkpoint inhibitors have been studied targeting the programmed cell death protein 1 (PD-L1) and an antibody-targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression and its potential effects against immune infiltration DTs. Two agents, nivolumab (PD-1) and ipilimumab (CTLA-4), are being investigated in a large multicohort trial recruiting patients with rare forms of cancers, including DTs.[30,32,33]

Radiation

Radiation is an effective primary therapy option for patients who are not good surgical candidates or who decline surgery or those in whom surgical morbidity would be excessive. Radiotherapy in intra-abdominal DTs is also considered when medical therapies are not available or have failed. This therapy has been used for extra-abdominal DT with successful outcomes and durable local control of the disease when positive margins are noted in the resection specimens.

However, the data support radiotherapy for the treatment and control of intra-abdominal DTs is limited. Radiation therapy for intra-abdominal DTs is mostly used as adjunct therapy after surgical resection with positive margins, which has been proven to decrease tumor relapse rates. Most trials have been performed in patients with positive margins after surgical excision. In one study, radiation alone vs surgical management alone provided a 78% compared to 61% local control of disease.[34] However, significant complications were observed in these studies including tissue fibrosis and radiation enteritis. The recommended dose of radiotherapy is 50–56 Gy over 5–7 weeks at 1.8–2 Gy per fraction, which has been proven to control disease in 74% of patients. Local recurrence rates do not appear to be reduced using higher doses. Higher doses are associated with an increased risk of complications (radiation enteritis) without improved local control.[35,36] Radiation would clearly complicate and often preclude further surgical attempts at resection and possibly even intestinal transplantation (IT).

Surgical Management

Indications

Surgical management is only considered in cases of extensive disease (Stage III, IV) with severe dysfunction (pain), good potential for resectability (tumors that do not involve vital organs or vascular components), impending morbidity of the disease (life-threatening conditions such as ischemia, perforation, or obstruction), when medical management has failed, and when rapid growth is present. The goal of surgical management is to offer improvement of the symptoms with total resection of the tumor with free margins after resection, but in some instances, this is unable to be achieved (eg, encasement of vascular structures by the tumor) and radical surgical procedures are often considered if medical therapy has failed. Often, multidisciplinary surgical approaches are necessary (ie, general surgery and urology teams for instance if ureters are encased by the DT).

Partial Surgical Resection

Despite achieving short-term remission after surgical excision with free margins, surgical procedures are performed only when absolute indications exist considering the high recurrence rate of DTs. Limitations to the surgical approach of DTs include an increased risk for iatrogenic complications, such as inadvertent enterotomies or ureteral injuries and when resection would lead to functional limitation resulting in increased morbidity and mortality. Moreover, surgical resection of mesenteric DTs may have appreciable morbidity and mortality since DTs tend to grow at the base of mesenteric vessels and small bowel with concomitant moderate blood loss occurring intraoperatively and occasional short bowel syndrome related to large segments of small bowel resected. Some recurrent DTs tend to have a more aggressive behavior than de novo DTs.[37]

Recently, ex vivo resection and intestinal autotransplantation surgery have provided solutions to the constraints of conventional surgery. The benefit of ex vivo transplantation is the excellent exposure of surgical field, optimum control of the critical step of tumor resection in a bloodless field, clear visualization of vascular pedicles and arches to protect normal tissues, and to ensure accurate excision. However, this technique faces certain barriers such as involvement of multiple organs, prolonged operative time, and increased frequency of blood transfusion. Patients with high-grade malignancy and those with extensive disease that encases small bowel may not be eligible for this approach.[34,37,38]

Intestinal Transplantation

IT is considered in patients with extensive disease and tumor encasement to nearby vascular structures and contiguous vital organs who are not eligible or who have failed medical therapy. DTs are the fourth most common indication for IT world-wide. IT is considered curative but a multidisciplinary team approach is necessary due to the potentially complex intraoperative disease burden that may involve urological and vascular structures. Multivisceral transplantation may sometimes be necessary as total abdominal evisceration might be required.[38,39]

A trial performed at the University of Miami with 14 cases of DTs after intestinal transplant showed a 5-year survival rate of 69.9%. However, 3 of 14 cases had DT recurrences after transplant which were successfully treated with partial resection. In this study, DT recurrences were seen to be dependent and confined to the recipient's native tissue (abdominal, thoracic muscle wall) with no recurrences noticed in the allograft. In other study performed in the University of Pittsburgh Medical Center based on 24

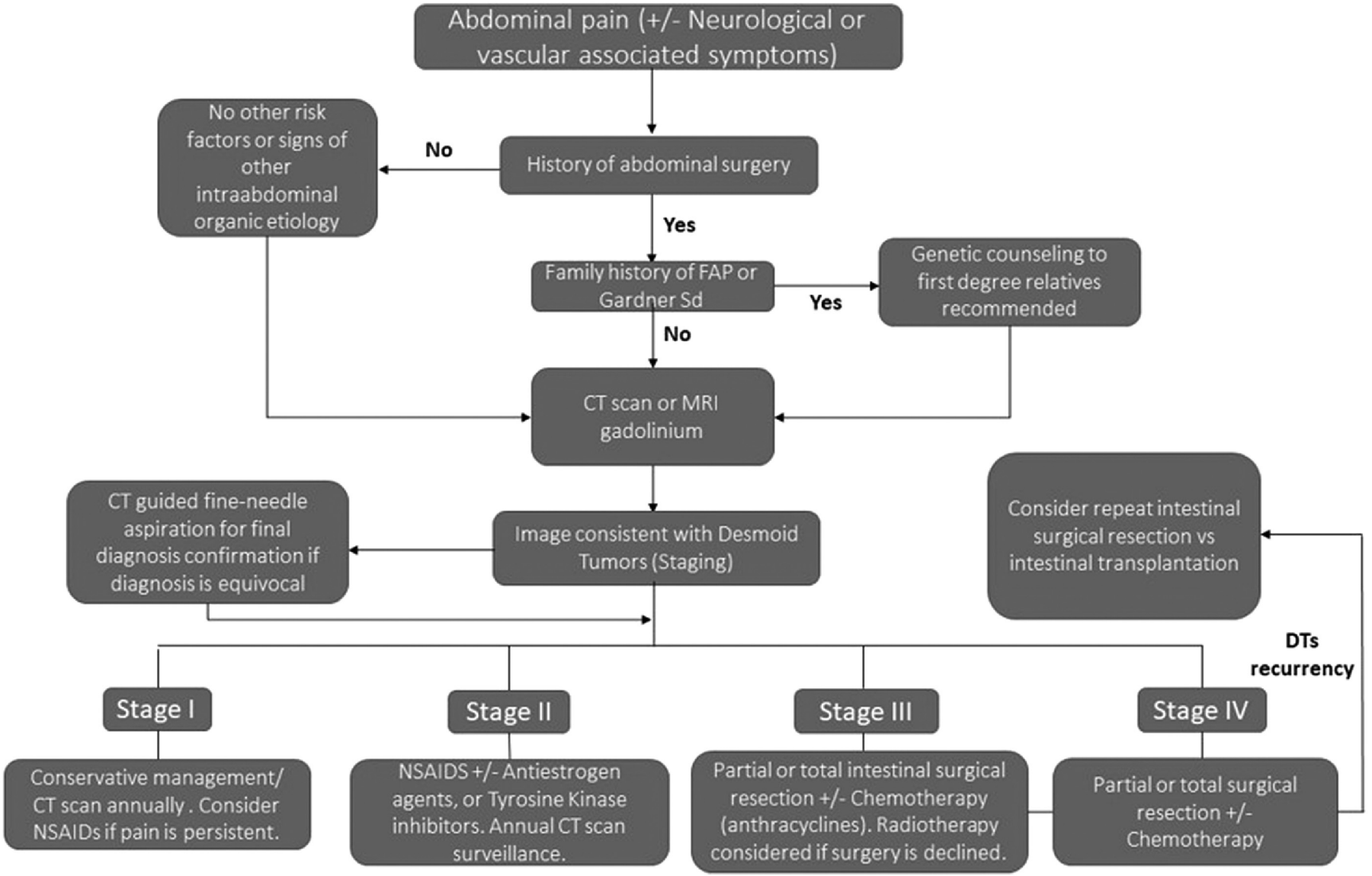

Figure 5. Diagnostic and treatment algorithm for Desmoid Tumors.

patients who underwent IT for DTs there was an 8% recurrence of DT with a 5-year survival rate of 61%. Results were likely influenced by the fact that patients were referred when they had more advanced disease. Retransplantation for recurrent DT has also been necessary. For patients with recurrent DTs, systemic medical therapy such as a chemotherapeutic regimen of doxorubicin, dacarbazine, and carboplatin may be effective in controlling the tumor burden and progression. However, prevention of recurrence of DTs has not been found to be effective with medical therapies in larger cohort trials except for case reports in the literature.[40]

New Promising Therapies

New efforts have been undertaken to study microenvironments of DTs which have served in the past to identify markers of genetic susceptibility and disease monitoring in breast, kidney, head and neck, lung, and liver cancer. The micro-environment is particularly relevant for DTs which lack the ability to metastasize.[41]

The metabolites that have been found to be appreciably different in the normal and desmoid tissues involve the aminoacyl-tRNA biosynthesis in the mitochondria and cytoplasm. The amino acids and lipids were found in greater concentration in the DT cell lines had greater concentrations. The differences in the amino acid concentrations may be an indicator that there is dysfunction in aminoacyl-tRNA synthetases (ARSs) which are responsible for protein translation, catalyze the ligation of amino acids to their cognate tRNAs, and interact with various proteins with tumorigenesis implications. Aspartate, glycine, and tyrosine were amino acids that were greater in the normal cells compared to the DT. ARS have been previously studied to target one ARS vs the others using known binding motifs; future screening experiments would target several ARS inhibitors against these cell lines to find most efficacious results.[42]

Another differentiated pathway is signal transduction amino acid–dependent mTORC1 activation pathways. mTORC1 has been shown to play a role in cell proliferation and tumor growth in transgenic animals carrying APC mutations such as those seen in DTs. Sirolimus is an mTOR inhibitor and is currently being investigated in a pediatric DT clinical trial (NCT01265030).[43]

The p53 pathway was recently identified as regulating Wnt/beta-catenin signaling in mesenchymal progenitor cells. Data have shown that overexpression of p53 and Ki-67 portends a high probability of recurrence, while high expression of both beta-catenin and p53 are markers for risk reduction. Further studies are needed to evaluate the role of NAMPT and p53 mutations in the pathogenesis and management of these mesenchymal tumors.[44]

Conclusion

DTs are uncommonly occurring benign tumors that rarely have clinical manifestations but they can have devastating complications when they occur. Familial-related conditions such as FAP or Gardner's syndrome should always be considered with the identification of intra-abdominal DTs. Despite DT typically growing quite slowly, it is important to educate the patient and perform appropriate work up and surveillance of DTs to avoid catastrophic outcomes and critical life-threatening complications. Medical management is always preferred over surgical management in view of being noninvasive, better tolerated, and having proven efficacy with durable local tumor control and growth retardation. Nevertheless, when surgical management is indicated, its success is adequate in the short term but there is a risk of DT recurrence even after multiple resections and multivisceral transplantation is sometimes necessary. Further studies are required to characterize the role of immunosuppression in the recurrence of DT and long-term survival rates after IT (Figure 5).

Websites such as www.desmoidtumors.com are resources to spread awareness and serve to create a database of patients' experiences and a clinical database that may serve as the blueprint for new robust clinical trials that could solidify existent and ongoing knowledge of the effectiveness of future drugs in the making for the management of DTs.[45]

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Correspondence:
Address correspondence to: Carlos J. Figueredo, MD, Department of Gastroenterology and Hepatology, Montefiore Medical Center, 697 Bronx River Road. Apt 301, Yonkers, New York 10704. e-mail: cfiguere@montefiore.org.

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