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Review

Desmoid-type fibromatosis

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Identity

Other names

Desmoid tumor
Desmoid
Aggressive fibromatosis
Deep musculoaponeurotic fibromatosis
Well differentiated nonmetastasizing fibrosarcoma
Invasive fibroma of Lec'ene and Delamare
Fibrosarcoma grade I of the desmoid type

Note

Desmoid-type fibromatoses are defined by the World Health Organization as 'clonal fibroblastic proliferations that arise in the deep soft tissues and are characterized by infiltrative growth and a tendency toward local recurrence but an inability to metastasize (Fletcher et al., 2002)'. This entity was first described in the 1800's by MacFarlane (Hosalkar et al., 2008). Muller later used the term desmoid, derived from the Greek word 'desmos', meaning tendon-like (Pakos et al., 2005) to refer to this lesion.

Classification

Fibromatoses may be classified as superficial or deep type based on location. Although superficial and deep fibromatoses share similiar histologic morphology of a fibroblastic proliferation, superficial-type fibromatoses occur at palmar, plantar, or penile locations as opposed to deep-seated, visceral and extra-abdominal axial locations (i.e. chest or abdominal wall) of the deep-type or desmoid-type. Additionally, superficial-type fibromatoses have different epidemiologic and molecular characteristics. For instance, superficial-type fibromatoses are more frequent than desmoid-type, and tend to occur more frequently in males. Superficial-type fibromatoses are less aggressive than desmoid-type fibromatoses (DTF). This may relate to a varied molecular biology underlying these two types. Although both types involve aberrances of the Wnt signaling pathway, the superficial-type generally lacks the β-catenin and APC gene mutations associated with DTF (Dolmans et al., 2011; Montgomery et al., 2001).

DTF can be further classified based on the site of involvement into extra-abdominal, abdominal, and intra-abdominal fibromatoses. Extra-abdominal fibromatoses more commonly occur on the chest, shoulder, back, thigh and head and neck. Abdominal fibromatoses arise typically from the rectus or internal oblique muscles and fascia in young pregnant or parous women. Intra-abdominal fibromatoses involve the mesentery or pelvis, and may be sporadic or associated with Gardner syndrome.

The majority of DTF arise sporadically, however others may be associated with germline mutations acquired in an autosomal dominant manner, such as Familial Adenomatous Polyposis (FAP) syndrome. FAP, which is caused by mutations in the adenomatous polyposis coli (APC) gene on chromosome 5, predispose patients to development of colorectal polyps that often progress to carcinoma. A variant of FAP, called Gardner syndrome is associated with extraintestinal manifestations such as DTF, as well as osteomas and epidermal cysts. Approximately 10% of these patients are affected by DTF (Gurbuz et al., 1994; Nieuwenhuis et al., 2011). Gardner fibromas are benign soft tissue lesions that are histologically similar to DTF, and represent precursor lesions (Coffin et al., 2007). They occur in infants and children, and 45% of patients with Gardner fibroma develop DTF. Thus, identification of Gardner fibromas in children is important as it may be the first indication that the patient has an underlying APC gene germline mutation. Close monitoring for extraintestinal manifestations of Gardner syndrome and

colorectal carcinoma are then warranted (Fletcher et al., 2002). Other described hereditary syndromes include the autosomal dominant inheritance of hereditary desmoid disease (HDD), also known as familial infiltrative fibromatosis, in which the literature describes various family presentations related to APC gene mutations (Couture et al., 2000; Maher et al., 1992; Scott et al., 1996). For example, Eccles et al. described a family with a 3' APC gene mutation (codon 1924) with somatic loss of wild-type APC where affected individuals exhibit multifocal desmoid tumors in conventional locations, as well as in the paraspinal muscles, arms, occiput, and breast. Interestingly, the FAP-associated colonic features were absent (Eccles et al., 1996). This family was later described to have an attentuated FAP syndrome.

Clinics and pathology

Disease

Desmoid-type fibromatosis

Phenotype / cell stem origin

Studies have shown that DTF are composed of spindle-shaped fibroblastic cells that express the intermediate filament vimentin but lack expression of epithelial markers. The location, cellular morphology, and immunoprofile of these tumors suggest that they derive from mesenchymal sources. However, the exact cell origin of DTF is unclear yet. Recent evidence demonstrates that DTF are derived at a cellular level from mesenchymal stem (progenitor) cells. In a mouse model that was genetically predisposed to develop DTF, the number of tumors formed was proportional to the number of mesenchymal stem cells (Wu et al., 2010). Another study showed that interferon type-1 is involved in the tumorigenesis of DTF potentially through modulating mesenchymal progenitors (Tjandra et al., 2007).

Etiology

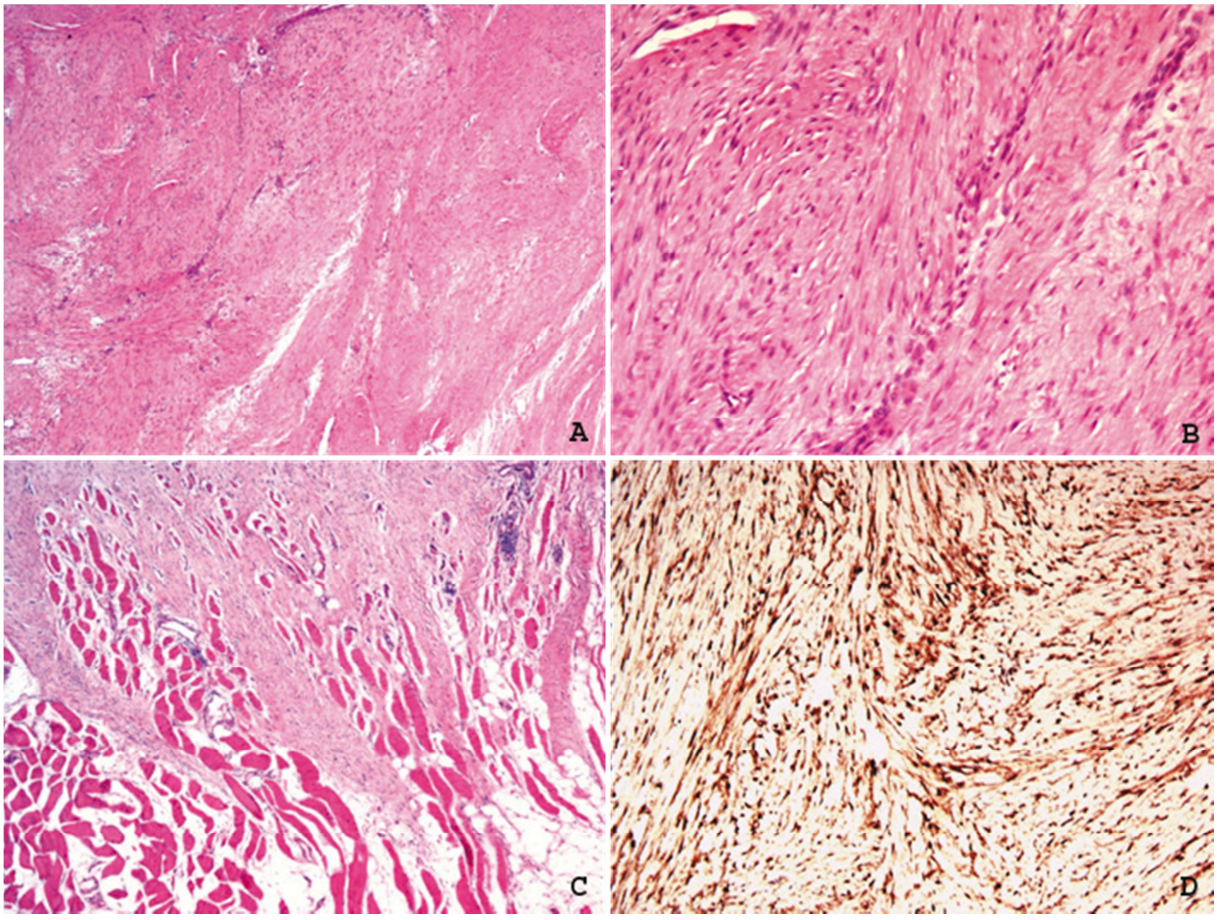
The etiology of DTF is multifactorial, including genetics, hormones, antecedent trauma and other risk factors. Mutations in both β-catenin and APC genes have been implicated in the pathogenesis of DTF. The association of DTF in patients with the FAP variant Gardner syndrome also suggests a genetic predisposition. Additionally, given the relationship of abdominal and intra-abdominal DTF in young women, high estrogren states were suspected to contribute to DTF pathogenesis. Studies examining expression of estrogen receptors (ERα and ERβ), progesterone receptor (PR), and androgen receptor (AR) in DTF found that the majority express ERβ but not ERα (Deyrup et al., 2006; Mignemi et al., 2012; Santos et al., 2010), although some DTF express ERα (Ishizuka et al., 2006). PR expression was varied with one study showing expression (Ishizuka et al., 2006) and others demonstrating lack of expression (Leithner et al., 2005; Mignemi et al., 2012; Santos et al., 2010). AR expression was detected in DTF (Hong et al., 2011; Ishizuka et al., 2006; Mignemi et al., 2012) and testosterone was found to have the ability to regulate beta-catenin protein level and proliferation rate in DTF (Hong et al., 2011). Given the expression of hormone receptors in DTF, antihormonal therapies seem like reasonal targets. Interestingly, tamoxifen, which binds ERα, has shown clinical promise despite the lack of ERα expression in most DTF studies. Also, trauma has been suggested as a risk factor, for example, status-post surgical procedures. Women status-post Cesarean section have been described to develop DTF in their surgical scars (De Cian et al., 1999; Li et al., 2012). Additionally, FAP patients status-post prophylactic colectomy develop DTF at surgical sites (Nieuwenhuis et al., 2011).

Epidemiology

Desmoid-type fibromatoses are rare, accounting for less than 0.03% of all neoplasms, and less than 3% of soft tissue neoplasms (Escobar et al., 2012; Reitamo et al., 1982). Incidence of DTF is estimated at 2-4 per million per year. They occur more frequently between 15-60 years of age, and are rare in children and the elderly. The abdominal type has a predilection for women, while the other types (extra-abdominal and intra-abdominal) have no sex predilection.

Clinics

The clinical presentation is variable depending on location and extent of the lesion. Patients with intra-abdominal DTF, particularly mesenteric lesions, may complain of some mild abdominal pain or simply an asymptomatic abdominal mass. Less frequently, these patients may present acutely with bowel perforation, obstruction, or gastrointestinal bleeding as a result of local desmoid tumor invasion. In a young woman with a pelvic mass, care must be taken clinically to distinguish between a DTF and gynecologic lesions such as an ovarian neoplasm or uterine leiomyoma/leiomyosarcoma. Patients with extra-abdominal DTF may complain of a slow-growing, deep-seated, firm, painless or minimally painful mass. Alternatively, depending on lesion location, patients may complain of neurologic symptoms or even decreased mobility if joints are involved. The clinical behavior of DTF is varied, with some lesions spontaneously regressing.



Desmoid-type fibromatoses. Figure A (lower power) and B (higher power): Bland spindle-shaped fibroblastic cells arranged in ill-defined fascicles. **Figure C:** The tumor invading adjacent skeletal muscle and adipose tissue with infiltrating border. **Figure D:** Immunohistochemistry showing positive nuclear β-catenin staining.

Pathology

Grossly, DTF are firm and display a white, whorled cut surface which may be poorly circumscribed. Microscopically, the lesion is a proliferation of bland appearing spindle-shaped fibroblasts in a collagenous stroma with infiltrative borders (Figures A, B and C).

Mitoses are rare and no atypia is seen. Keloid-like collagen or extensive hyalinization may be present. DTF, especially those arising in the mesentery and pelvis, may show extensive myxoid change or may have fasciitis-like morphology.

DTF stain positive for vimentin and variably positive for smooth muscle actin or other muscle-specific markers by immunohistochemistry. Rare cells may also be positive for S100 protein.

Nuclear staining for β-catenin by immunohistochemistry (Figure D) is positive in at least 80% of sporadic DTF, with some studies demonstrating 98% nuclear staining (Carlson and Fletcher, 2007; Lazar et al., 2008). Therefore, β-catenin is extremely useful in distinguishing DTF from other spindle cell neoplasms.

The differential diagnosis of DTF is broad, encompassing both benign and malignant entities. For example, extra-abdominal DTF are sometimes histologically similar to keloids and nodular fasciitis (both benign processes) as well as low-grade fibromyxoid sarcomas (which appear benign-looking but have the ability to metastasize). Intra-abdominal DTF are most commonly misdiagnosed as gastrointestinal stromal tumors (GIST) (Huss et al., 2013). However, the presence of nuclear β-catenin supports a diagnosis of DTF, although a minority of GIST may demonstrate some nuclear β-catenin positivity. Additional stains may be used to distinguish between DTF and GIST, such as c-kit and DOG-1 (Discovered On GIST-1). c-kit and DOG-1 are positive in GIST, but negative in DTF though an infiltrate of mast cells within DTF can result in positive c-kit staining. Other differential diagnoses for intra-abdominal DTF may include low-grade dedifferentiated liposarcoma, solitary fibrous tumor (SFT), inflammatory myofibroblastic tumor, and idiopathic retroperitoneal fibrosis (Ormond's disease).

Low-grade sarcomas, such as a low-grade dedifferentiated liposarcoma with minimal atypia, should be considered, as it has a similar infiltrative growth pattern. MDM2 immunohistochemistry or Fluorescence In Situ Hybridization (FISH) study may

be helpful to distinguish. Solitary fibrous tumors lack the fascicular pattern of DTF and classically have staghorn vessels. However, if presented with a small biopsy, it may be difficult to distinguish, but SFT will positively stain for CD34, CD99, and Bcl-2 whereas DTF will not. Inflammatory myofibroblastic tumor usually is more cellular, has less collagen and an inflammatory infiltrate consisting of plasma cells, lymphocytes, and eosinophils. Half of inflammatory myofibroblastic tumor cases have an anaplastic lymphoma kinase (ALK) gene rearrangement and will thus express ALK, while DTF will not. Histologically, idiopathic retroperitoneal fibrosis, recently categorized as one of the IgG4-related diseases (Deshpande, 2012; Fujimori et al., 2013), may look similar to DTF but the hyalinized collagen is more prominent, and typically a lymphoplasmacytic infiltrate is present. DTF may occasionally have a lymphoplasmacytic infiltrate, however retroperitoneal fibrosis will not stain for β-catenin.

Treatment

The clinical course of DTF is variable with some lesions spontaneously regressing and others rapidly progressing locally with the potential to obstruct vital structures. Given this unpredictable clinical course, treatment should be individualized and may use multiple modalities. Historically, the mainstay of treatment has been surgery with the goal of negative margins in a patient amenable to resection. However, DTF often recur after resection, even when negative margins have been obtained (Melis et al., 2008). Current guidelines proposed by the National Comprehensive Cancer Network (NCCN) recommend observation alone initially for patients with small tumors, especially if surgery would lead to significant morbidity (von Mehren et al., 2012). A retrospective study by Fiore et al. supports this assessment as they found that a watchful waiting approach benefited half of their patients with DTF (Fiore et al., 2009). Radiation has been used both pre- and post-surgical resection. Results regarding use of neoadjuvant radiotherapy are still not well-established as large trials are limited. Patients with positive margins status post-surgical resection have typically received radiation therapy, however there is no consensus to this approach. Some large trials fail to show benefit from post-surgical radiation therapy (Nuyttens et al., 2000; Spear et al., 1998). The NCCN recommends post-operative radiation for large DTF, however this is not clearly defined. Clinicians must also be aware that radiation therapy may result in secondary malignancies and should be administered with caution.

Systemic medical therapy is an additional option which includes the use of hormonal therapy, non-steroidal antiinflammatory agents, tyrosine kinase inhibitors, interferon, and cytotoxic chemotherapy, however prospective data on the success of such treatment are lacking. For instance, given the expression of hormone receptors in DFT, antihormonal therapies (tamoxifen, toremifene, raloxifene, progesterone, megestrol, tesolactone) have been effective in case reports and small series. Antiestrogens have been described to have a response rate of roughly 50% (Bocale et al., 2011). Few large-scale studies have examined the role of other hormonal therapies but success in case reports are promising.

DTF pathogenesis involves Wnt signaling pathway abnormalities triggering COX-2-mediated activation of Platelet derived growth factor receptor-alpha (PDGFRA) and platelet derived growth factor receptor-beta (PDGFRB). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit COX-2 and thus may benefit affected patients. NSAIDs such as sulindac and indomethacin have been reported to have partial and complete responses at rates of 37%-57% (Escobar et al., 2012). Although expression data of the receptor tyrosine kinases (c-kit, PDGFRA, PDGFRB) are conflicting, patients with DTF were reported to respond to the tyrosine kinase inhibitors imatinib or sorafenib. A large phase II trial testing imatinib in patients with progressive and recurrent DTF demonstrated complete and partial responses, and a 67% nonprogression rate (Penel et al., 2011). Similarly, a sorafenib study showed stable disease in 70% of patients, and partial response in another 25% (Gounder et al., 2011).

Data examining the success of interferon are limited, but individual case reports have been published (Stengel et al., 2008). Moreover, despite the often slow growth of DTF, chemotherapy has shown success. A recent study showed that chemotherapy (largely combination chemotherapy) in patients resistant to many other treatments showed approximately 80% response (complete response in 2%, partial response in 20%, and stable free progression in 60%) (Garbay et al., 2012).

Prognosis

DTF are locally invasive, but non-metastatic. Local DTF recurrence rates after initial management range from 20-40% (Ballo et al., 1999; Huang et al., 2009; Lev et al., 2007; Nuyttens et al., 2000). Current research is focused on identifying prognostic indicators. In one of the largest retrospective reviews to evaluate prognosis in patients with sporadic DTF, Salas et al. identified age (< 37 years-old), large size of the tumor (> 7 cm), and extra-abdominal location as being associated with poor prognosis (Salas et al., 2011). This study focused on sporadic DTF, and excluded examination of DTF from Gardner syndrome patients to retain a homogenous population.

Further work aimed at identifying molecular prognostic indicators has been reported. For example, Lazar et al. specifically examined CTNNB1 point mutations (T41A, S45F, S45P) associated with sporadic DTF and found that S45F mutations were associated with an increased tendency of recurrence after initial resection. With this knowledge, patients with S45F mutations

might be managed differently. Future genotyping to determine specific CTNNB1 mutations may prove quite useful in diagnosis and management of patients with DTF (Lazar et al., 2008). Recently, overexpressed genes in DTF have been identified by gene expression profiling. Colombo et al. examined a subset of genes which contain TCF/LEF binding promoter motifs likely representing direct targets of transcriptional activation by β-catenin/TCF. The group narrowed their search to include the midkine gene. Midkine expression was present in roughly half of the DTF samples examined. In addition, they correlated midkine protein expression with DTF recurrence and found that it was associated with increased local recurrence, as well as a shorter time to recurrence (Colombo et al., 2011).

Genetics

Note

Eighty-five percent of DTF result from sporadic point mutations in the CTNNB1 gene which encodes β-catenin (Lazar et al., 2008). Point mutations of CTNNB1 (such as T41A, S45F, S45P) lead to mutated β-catenin that is resistant to degradation by a complex comprised of APC, axin, and glycogen synthase kinase-3β. As a result, β-catenin accumulates in the cytoplasm, translocates to the nucleus, and aids in activation of Wnt signaling pathway target genes involved in tumorigenesis (Akiyama, 2000).

Both sporadic and germline mutations in the tumor suppressor gene APC have also been described in DTF (Lips et al., 2009). As described above, APC forms part of a complex which targets β-catenin for degradation. When APC is mutated, this complex does not form properly leading to β-catenin accumulation and thus increased transcription of Wnt signaling pathway target genes. Germline mutations of APC are associated with FAP, an autosomal dominant condition characterized by thousands of colonic polyps which can progress to colon cancer. The occurrence of DTF in FAP patients is roughly 10% (Gurbuz et al., 1994; Nieuwenhuis et al., 2011). These patients are at increased risk for DTF as 1 APC allele is already mutated and if a sporadic APC mutation occurs, they become susceptible to the development of DTF. APC mutations have frequently been found in sporadic cases as well, with more than 400 mutations identified, 95% of which result in a truncated APC protein. APC is a large protein with most DTF-causing mutations occurring between codons 1445-1578 (of 2843 total codons). Reports of severe desmoid phenotypes such as those associated with HDD result from APC truncation at the 3' end beyond codon 1578 (Lips et al., 2009).

Numerous studies have attempted to elucidate the molecular pathogenesis and to investigate the possible therapeutic targets of DTF in recent years, besides the studies on the above-mentioned APC/β-catenin/Wnt signaling pathway(s). Cyclooxygenase (COX-2), a target of Wnt signaling, has been described in the setting of multiple tumorigenesis models as activation results in apoptosis inhibition, angiogenesis stimulation, and an increase in various growth factors. In DTF, β-catenin interacts with T-cell factor (TCF) to enhance COX-2 expression. COX-2 in turn leads to constitutive coactivation of platelet derived growth factor receptors (Signoroni et al., 2007).

PDGFRA and PDGFRB along with c-kit belong to a class of receptor tyrosine kinases which can be selectively targeted by tyrosine kinase inhibitors such as imatinib or sorafenib. Selectively targeting PDGFRs with imatinib or sorafenib as has been demonstrated in treatment of GIST (Casali et al., 2012) or COX-2 with NSAIDs have shown effectiveness in treating DTF as mentioned in the Treatment section. Despite the intuition that COX-2 and tyrosine kinase inhibitors would benefit DTF patients, expression studies of PDGFRA, PDGFRB, and c-kit in DTF are conflicting. Some studies show expression of both PDGFRA and PDGFRB (Mace et al., 2002; Signoroni et al., 2007), while others show only PDGFRA expression (Liegl et al., 2006) or PDGFRB expression (Cates et al., 2012). Similarly, some studies demonstrate c-kit expression in DTF (Mace et al., 2002) while others do not (Santos et al., 2010; Signoroni et al., 2007). There are multiple explanations for these findings such as heterogenity among DTF, as well as different methodologies for determining expression, including use of different antibodies (Miettinen, 2001) or use of tissue from formalin-fixed, paraffin-embedded tissue versus fresh tissue. It should be noted that patients with DTF demonstrating c-kit exon 10 variants (M541L and V530I) responsive to imatinib have been reported, however, sample size is small and evidence that these specific mutations result in c-kit activation is limited. Moreover, the M541L variant has been described as a polymorphism (Dufresne et al., 2010; Goncalves et al., 2006; Kurtz et al., 2012; Tamborini et al., 2006).

Cytogenetics

Note

Trisomy 8 and trisomy 20, as well as loss of 5q (location of APC gene) have been associated with desmoid-type fibromatosis (Bridge et al., 1996; De Wever et al., 2000; Qi et al., 1996). More recently, Salas et al. used array comparative genomic hybridization to confirm and further characterize chromosomal anomalies associated with DTF (Salas et al., 2010). However, the majority of these studies examined sporadic DTF rather than FAP-associated DTF. Robanus-Maandag et al. also used array comparative genomic hybridization together with multiple-ligation dependent probe amplification to compare chromosomal aberrations between sporadic and FAP-associated desmoid tumors. The authors found that overall, DTF had a limited number of genetic changes. Gains at 8q and 20q were found more commonly in sporadic DTF while 5q losses were

commonly identified in FAP-associated DTF. Interestingly, loss of a region of 6q was associated with both sporadic and FAP-associated DTF (Robanus-Maandag et al., 2011). Future studies of this region may reveal insights into DTF pathogenesis.

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