

Cancer Association of South Africa (CANSA)



Fact Sheet on Desmoid-Type Fibromatosis

Introduction

Desmoid tumour commonly develops in the fibrous (connective) tissue of the body that forms tendons and ligaments, usually in the arms, legs or midsection, and also in the head and neck. These tissues of the body connect, support, and surround other body parts and organs. The myofibroblast is the cell considered to be responsible for the development of desmoid tumour. Regardless of its scientific classification, a desmoid tumour can be invasive to surrounding tissues and difficult to control.

[Picture Credit: Desmoid-type Fibromatosis]



Desmoid tumours can develop virtually at any body site. Superficial desmoids tend to be less aggressive than deep desmoids (abdominal, extra abdominal, mesenteric). These tumours look like dense scar tissue and just like scar tissue, they adhere tenaciously to surrounding structures and organs, and, thus they are commonly difficult to remove. Surgery has been the traditional main mode of therapy for desmoid tumours but up to 20-50% of these tumours recur after surgery.

Desmoid tumour is called an aggressive fibromatosis as it has similarities with a malignant (cancerous) tumour called fibrosarcoma. However, it is considered benign because it does not metastasise (spread) to other parts of the body.

Synonyms include:

- aggressive fibromatosis
- deep fibromatosis
- musculoaponeurotic fibromatosis
- non-metastasising fibrosarcoma

Desmoid-type Fibromatosis is defined by the World Health Organization as clonal fibroblastic proliferations that arise in the deep soft tissues and is characterised by infiltrative growth and a tendency toward local recurrence but an inability to metastasise'.

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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Martinez, T.J., Pajares, B.T., Torres, R.I., Hernando, C.J. & Pazo, C.R. 2017.

“Desmoid-type fibromatosis is a sarcoma subtype that gathers some singular characteristics, making it a difficult challenge to face in clinical practice. Despite its excellent survival prognosis, these tumors may be unpredictable, ranging from an asymptomatic indolent course to persistent, local, and extended recurrences that significantly impair quality of life. Although surgery was initially considered the first elective treatment, collected published data during the past few years are now pointing to the "wait and see" approach as a reasonable initial strategy because many patients can live a long life with the disease without having symptoms. When symptoms appear or there is a risk of functional impairment, a wide spectrum of therapies (local and systemic) can be useful in improving symptoms and controlling the disease. Because of the low incidence of desmoid-type fibromatosis, there is scarce scientific evidence supporting any specific treatment. Nonetheless, if volumetric responses are needed, chemotherapy may be a reasonable early option. However, if long-term control of disease is desirable, hormonal therapy, NSAIDs, and TKIs are the likely treatments of choice. Recent new findings in the biologic development of these tumors, such as the role of Wnt/ β -catenin dependent pathway, have shown that the prognostic information provided by specific CTNNB1 gene mutations and other genetic profiles can lead to better methods of selecting patients as candidates for other approaches. Based on recent research, the Notch pathway inhibition in DF is one of the most promising potential targets to explore. As an orphan disease, it is mandatory that as many patients as possible be included in clinical trials.”

Epidemiology of Desmoid-type Fibromatosis (FAP)

- ~0.03% of all neoplasms; < 3% of all soft tissue tumours
- 10 - 30% of familial adenomatous polyposis (FAP) patients have desmoid type fibromatosis (also called Gardner syndrome); 7.5 - 16% of patients with fibromatosis have FAP
- Mean age: 36 - 42 years
- Female predominance from puberty to age 40; younger and older patients have M:F = ~1:1
- Male predominance in FAP of 3:1

Incidence of Desmoid-type Fibromatosis (FAP)

Because Desmoid-type Fibromatosis is not a malignant condition, the National Cancer Registry (2017) does not provide any information regarding its incidence.

Signs and Symptoms of Desmoid-type Fibromatosis (FAP)

Desmoid tumours typically affect tissue that is elastic and easily moved, a tumour may exist for a long time before being discovered, growing large and pushing aside surrounding tissue. While each child or adult may experience symptoms differently, the following are the most common symptoms of desmoid tumours. The symptoms of desmoid tumours vary greatly depending on size, location, and spread of the tumour. Some of the common symptoms include the following:

- A painless swelling or lump
- Pain or soreness caused by compressed nerves and/or muscles
- Pain and obstruction of the bowels
- Limping
- Other difficulty using legs, feet, arms or hands

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- Difficulty of using other affected parts of the body

Diagnosis of Desmoid-type Fibromatosis (FAP)

X-ray – Use of X-radiation to take images of dense tissues inside the body such as bones or tumours

Ultrasound - A scan that uses soundwaves to create images from within the body.

CT - The Computer Tomography (CT) scan takes a number of X-rays to make a 3D images of an affected area.

MRI - Magnetic Resonance Imaging (MRI) uses magnets to create an image of the tissues inside the body.

Histopathology - Examination of a tissue sample by a pathologist under a microscope to identify disease. The tissue sample can be taken during a biopsy or from a tumour removed during surgery.

Zhou, L., Xu, H., Zhou, J., Dong, L., Zhang, P., Yang, X. & Wasng, C. 2019.

BACKGROUND: Desmoid-type fibromatosis (DTF) is a lesion characterized by clonal proliferation of myofibroblasts, which exhibits an infiltrative growth pattern. It is necessary for them to be distinguished from other fibroblastic and myofibroblastic lesions as well as spindle cell tumors. Altered Wnt signaling can act as a defining characteristic of DTF, with nuclear β -catenin serving as a diagnostic marker for. Transcription factor E3 (TFE3) has been linked to Wnt pathway activation and regulation, and may add value to the diagnosis of DTF. The present study, therefore, sought to assess whether TFE3 is a specific diagnostic marker for DTF.

METHODS: Nuclear TFE3 and β -catenin staining was performed on a wide range of tumor types such as DTF (n = 46), nodular fasciitis (n = 14), neurofibroma (n = 5), dermatofibrosarcoma protuberans (n = 5), gastrointestinal stromal tumor (n = 10), sclerosing epithelioid fibrosarcoma (n = 2), synovial sarcoma (n = 5), leiomyoma (n = 3) and cutaneous scar tissue (n = 4) using an immunohistochemical approach. In addition, the clinicopathological features and localization of these tumors were summarized. FISH assay was carried out to examine Xp11.2 translocations/TFE3 gene fusions. Statistical difference between immunohistochemical expression of TFE3 and β -catenin was analyzed.

RESULTS: The expression of nuclear TFE3 protein was found in 43 (93.5%) DTF tissue samples, ranging from moderate to intense expression levels. The distribution rates of TFE3 positivity in nodular fasciitis, gastrointestinal stromal tumor, leiomyoma and scar tissue samples were 42.9, 40, 25 and 33%, respectively. All studied samples of neurofibroma, synovial sarcoma, sclerosing epithelioid fibrosarcoma and dermatofibrosarcoma protuberans were negative for TFE3.

CONCLUSIONS: This study reveal that TFE3 has a potential to serve as a diagnostic marker capable of assisting in the differential diagnosis of DTF and other spindle cell lesions.

Differential diagnosis

The differential diagnosis is broad with fibrosarcomas on the one extreme and myofibroblastic processes such as nodular fasciitis and even hypertrophic scars and keloids on the other. The differential diagnosis of intra-abdominal DTs includes gastrointestinal stromal tumours, solitary fibrous tumours, inflammatory myofibroblastic tumours, sclerosing mesenteritis and retroperitoneal fibrosis (see these terms).

Prognosis of Desmoid-type Fibromatosis (FAP)

Local recurrence occurs in around 70 % of cases. Prognosis depends on the type of tumour. Life expectancy is normal for abdominal and extra-abdominal tumours. However, it is lower in cases of intra-abdominal DTs due to complications such as intestinal obstruction, hydronephrosis or sepsis. Repeated surgical resections are associated with a greater risk of morbidity.

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

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Management and treatment of Desmoid-type Fibromatosis (FAP)

Complete surgical resection remains the therapeutic mainstay of DTs. For unresectable tumours or those not amenable to surgical resection with RO (microscopic tumour clearance) intent or accompanied by an unacceptable function loss, non-surgical treatments comprise radiotherapy, anti-oestrogen therapy, non-steroidal anti-inflammatory agents, chemotherapy (e.g. methotrexate, vinblastine/vinorelbine, pegylated liposomal doxorubicin) and/or tyrosine kinase inhibitors (e.g. imatinib, sorafenib). As DTs have a variable and often unpredictable clinical course, a period of watchful waiting is advisable for asymptomatic patients. As DTs often recur, a surveillance strategy every 3-6 months is essential.

García-Ortega, D.Y., Martín-Tellez, K.S., Cuellar-Hubbe, M., Martínez-Said, H., Álvarez-Cano, A., Brenner-Chaoul, M., Alegría-Baños, J.A. & Martínez-Tlahuel, J.L. 2020.

Desmoid tumors represent a rare entity of monoclonal origin characterized by locally aggressive behavior and inability to metastasize. Most cases present in a sporadic pattern and are characterized by a mutation in the CTNNB1 gene; while 5-15% show a hereditary pattern associated with APC gene mutation, both resulting in abnormal β -catenin accumulation within the cell. The most common sites of presentation are the extremities and the thoracic wall, whereas FAP associated cases present intra-abdominally or in the abdominal wall. Histopathological diagnosis is mandatory, and evaluation is guided with imaging studies ranging from ultrasound, computed tomography or magnetic resonance. Current approaches advocate for an initial active surveillance period due to the stabilization and even regression capacity of desmoid tumors. For progressive, symptomatic, or disabling cases, systemic treatment, radiotherapy or surgery may be used. This is a narrative review of this uncommon disease; we present current knowledge about molecular pathogenesis, diagnosis and treatment.

Pannier, D., Cordoba, A., Ryckewaert, T., Robin, Y-M. & Penel, N. 2019.

"We review the role of hormonal therapy in the management of different conjunctive tumors. Progestin and aromatase inhibitors seem active in low-grade endometrial stromal sarcoma, but larger case-series are needed. There is no evidence to support the use of hormonal therapy as an adjuvant treatment for low-grade endometrial stromal sarcoma. We did not find relevant data on the use of hormonal therapy for other uterine sarcomas (e.g., high-grade endometrial sarcoma, undifferentiated uterine sarcoma, and adenosarcoma). Gonadotropin-releasing hormone agonist, anti-estrogens and aromatase inhibitor seem active in advanced aggressive angiomyxoma, but larger studies are warranted. The use of aromatase inhibitor in estrogen-receptor-positive uterine leiomyosarcoma requires further clinical investigation. There is no evidence supporting the use of hormonal therapy in desmoid-type fibromatosis. International collaboration efforts are warranted to better explore the role of hormonal therapies in management of estrogen-receptor-positive uterine leiomyosarcoma, low-grade endometrial stromal sarcoma, and aggressive angiomyxoma."

Timbergen, M.J.M., Smits, R., Grünhagen, D.J., Verhoef, C., Sleijfer, S. & Wiemer, E.A.C. 2019. Activated signalling pathways and targeted therapies in Desmoid-type fibromatosis: a literature review. *Front Oncol.* 2019 May 17;9:397. doi: 10.3389/fonc.2019.00397. eCollection 2019.

Desmoid-type fibromatosis (DTF) is a rare, soft tissue tumor of mesenchymal origin which is characterized by local infiltrative growth behavior. Besides "wait and see," surgery and radiotherapy, several systemic treatments are available for symptomatic patients. Recently, targeted therapies are being explored in DTF. Unfortunately, effective treatment is still hampered by the limited knowledge of the molecular mechanisms that prompt DTF tumorigenesis. Many studies focus on Wnt/ β -catenin signaling, since the vast majority of DTF tumors harbor a mutation in the CTNNB1 gene or the APC gene. The established role of the Wnt/ β -catenin pathway in DTF forms an attractive therapeutic target, however, drugs targeting this pathway are still in an experimental stage and not yet available in the clinic. Only few studies address other signaling pathways which can drive uncontrolled growth in DTF such as: JAK/STAT, Notch, PI3 kinase/AKT, mTOR, Hedgehog, and the estrogen growth regulatory pathways. Evidence for involvement of these pathways in DTF tumorigenesis is

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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limited and predominantly based on the expression levels of key pathway genes, or on observed clinical responses after targeted treatment. No clear driver role for these pathways in DTF has been identified, and a rationale for clinical studies is often lacking. In this review, we highlight common signaling pathways active in DTF and provide an up-to-date overview of their therapeutic potential.

Paul, A., Blouin, M.J., Minard, Colin, V., Galmiche, L., Coulomb, A., Corradini, N., Boutaroux, H., Van den Abbeele, R., Leboulanger, N., Denoyelle, F., Garabedian, E.N., Couloiganer, V. & Orbach, D. 2019.

INTRODUCTION: Desmoid-type fibromatosis (DF) is a rare benign lesion known for its local aggressiveness. The tumor management still remains under debate. Primary head and neck (HN), represents the second most prevalently affected site in children with DF. This study aims to analyze the specificity of HN-DF in children, focusing on long-term effects of the tumor and therapies.

METHODS: This retrospective multicenter study analyzed children treated for a HN-DF between 1993 and 2013. All medical files were reviewed and their outcomes analyzed according to the initial therapies provided.

RESULTS: Sixteen children were selected. Mandibular and submandibular areas were the main locations (11 cases). Eight children underwent chemotherapy as first-line therapy with tumor control in 3 cases and 5 cases needing additional treatment. Six children underwent primary surgery: isolated in 3 cases and with additional treatment after tumor progression in 3 cases. A wait-and-see attitude was adopted for 2 children without any additional treatment in 1 case, and followed by additional chemotherapy in the other case. Total burden of treatment to control the disease was a biopsy (1 case), surgery (3 unique cases, 1 multiple case), surgery with chemotherapy (6 cases), and exclusive medical therapies (5 cases). Surgical postoperative sequelae were facial palsy (cases of parotid gland affection), XIth cranial nerve sacrifice or sensory impairment.

CONCLUSION: HN-DF is a local and extensive disease that is difficult to control with surgery alone. Sequelae are frequent due to the initial tumor location or therapies. Initial conservative strategies need to be discussed in a multidisciplinary way in order to try to control the disease with the minimal morbidity.

Wang, Z., Wu, J., Tian, X. & Hao, C. 2019.

“Desmoid-type fibromatosis (DF) is a rare monoclonal fibroblastic proliferation that is characterized by locally infiltrative but rarely metastatic lesions. Tyrosine kinase and γ -secretase inhibitors are primarily used in the targeted therapy of DF. The use of these drugs, however, is mainly based on the recommendations of retrospective studies with small sample sizes. Previous studies that focused on the mechanism, efficacy, and safety of targeted therapy for DF were reviewed to provide references for clinical applications and research. The efficacy and safety of targeted therapy were compared with those of other systemic therapy options. Targeted therapy does not provide considerable advantages in efficacy and safety over other medical treatments and is usually applied after the failure of antihormonal therapies, nonsteroidal anti-inflammatory drugs, and chemotherapy. Further studies are required to explore the mechanism, indications, and appropriate drug dosage of the targeted therapy of DF.”

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

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The [South African National Clinical Trials Register](#) provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Sources and References Consulted and/or Utilised

Desmoid-type Fibromatosis

<https://rare-diseases.org/rare-diseases/desmoid-tumor/>
<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/desmoid-type-fibromatosis>
<http://atlasgeneticsoncology.org/Tumors/DesmoidFibromatosisID5179.html>
<https://sarcoma.org.uk/sarcoma-types/desmoid-type-fibromatosis>
<http://www.pathologyoutlines.com/topic/softtissuefibromatosisdeep.html>
<https://academic.oup.com/annonc/article/28/10/2399/3884601>
<https://pubs.rsna.org/doi/full/10.1148/rg.283075169>
<https://pubs.rsna.org/doi/full/10.1148/rg.2016150153>
https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=873
<https://www.sciencedirect.com/science/article/pii/S0009926015001609>
<http://iv.iarjournals.org/content/27/4/555.full>
<https://www.jbsr.be/articles/10.5334/jbsr.1612/>
<https://www.uptodate.com/contents/desmoid-tumors-epidemiology-risk-factors-molecular-pathogenesis-clinical-presentation-diagnosis-and-local-therapy>
<https://www.vumc.org/pmi-residents/publication/differential-diagnostic-considerations-desmoid-type-fibromatosis>

Desmoid-type Fibromatosis Picture

<http://iv.iarjournals.org/content/24/6/877/F1.expansion.html>

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Martinez, T.J., Pajares, B.T., Torres, R.I., Hernando, C.J. & Pazo, C.R. 2017. Desmoid-type fibromatosis: who, when, and how to treat. *Curr Treat Options Concol*. 2017 May;18(5):29. doi: 10.1007/s11864-017-0474-0.

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Orbach, D., Brennan, B., Bisogno, G., Van Noesel, M., Minard-Colin, V., Daragjati, J., Casanova, M., Corradini, N., Zanetti, I., De Salvo, G.L., Defachelles, A.S., Kelsey, A., Arush, M.B., Francotte, N. & Ferrari, A. 2017. The EpSSG NRSTS 2005 treatment protocol for desmoid-type fibromatosis in children: an international prospective case series. *Lancet Child Adolesc Health*. 2017 Dec;1(4):284-292. doi: 10.1016/S2352-4642(17)30045-7. Epub 2017 Sep 12.

Pannier, D., Cordoba, A., Ryckewaert, T., Robin, Y-M. & Penel, N. 2019. Hormonal therapies in uterine sarcomas, aggressive angiomyxoma, and desmoid-type fibromatosis. *Crit Rev Oncol Hematol*. 2019 Nov;143:62-66.

Paul, A., Blouin, M.J., Minard, Colin, V., Galmiche, L., Coulomb, A., Corradini, N., Boutaroux, H., Van den Abbeele, R., Leboulanger, N., Denoyelle, F., Garabedian, E.N., Couloiganer, V. & Orbach, D. 2019. Desmoid-type fibromatosis of the head and neck in children: a changing situation. *Int J Pediatr Otorhinolaryngol*. 2019 Aug;123:33-37. doi: 10.1016/j.ijporl.2019.04.037. Epub 2019 Apr 26.

Timbergen, M.J.M., Smits, R., Grünhagen, D.J., Verhoef, C., Sleijfer, S. & Wiemer, E.A.C. 2019. Activated signalling pathways and targeted therapies in Desmoid-type fibromatosis: a literature review. *Front Oncol*. 2019 May 17;9:397. doi: 10.3389/fonc.2019.00397. eCollection 2019.

Wang, Z., Wu, J., Tian, X. & Hao, C. 2019. Targeted therapy of desmoid-type fibromatosis: mechanism, current situation, and future prospects. *Front Med*. 2019 Feb 22. doi: 10.1007/s11684-018-0672-6. [Epub ahead of print]

Zhou, L., Xu, H., Zhou, J., Dong, L., Zhang, P., Yang, X. & Wasng, C. 2019. Nuclear TFE3 expression is a diagnostic marker for desmoid-type fibromatosis. *Dign Pathol*. 2019 May 1;14(1):34. doi: 10.1186/s13000-019-0814-4.