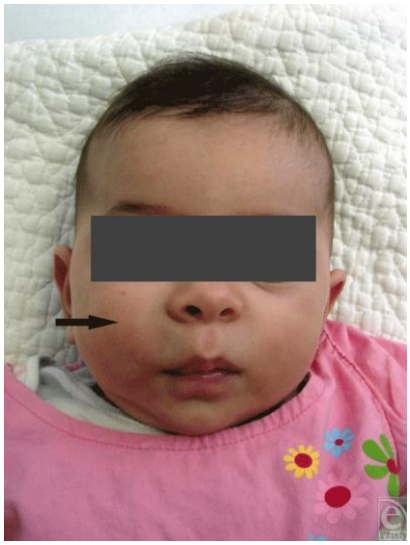
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Childhood Desmoid Tumour

Introduction

Childhood desmoid tumour, also called aggressive fibromatosis, is a tumour that develops in the fibrous tissue that forms tendons and ligaments, usually in the arms, legs or midsection, but also sometimes in the head and neck. Locally, a desmoid tumour is very similar to a malignant (cancerous) tumour called fibrosarcoma in that local recurrence is very high.



[Picture Credit: Childhood Desmoid Tumour]

However, a desmoid tumour is considered 'benign' because it does not metastasise (spread) to other parts of the body.

Regardless of its scientific classification, a desmoid tumour can be invasive to surrounding tissues and difficult to control. It can adhere to, and intertwine with, surrounding structures and organs.

Tayeb Tayeb, C., Parc, Y., Andre, T. &, Lopez-Trabada Ataz, D. 2020.
"About 15 % of patients with familial adenomatous polyposis "PAF" develop one or more desmoid tumors in their lifetime. These are benign mesenchymal tumors with local aggressivity but with no potential for metastases. Most of the desmoids tumors result from a sporadic genetic anomaly in the β catenin gene. When related to familial adenomatous polyposis or "PAF", this mutation is not present, and the patients must be sent in genetic counselling. The PAF is a dominant autosomic illness related to a germinal mutation in the APC gene. Sometimes, these tumors can be the first manifestation of the illness. The diagnosis in a context of PAF can be easily done by imaging, but a pathological confirmation is needed. These tumors raise a therapeutic problem because of their heterogeneity and the absence of predictive biomarkers along illness evolution. The identification of prognostic biological and clinical factors would make easier the selection of patients requiring first-line treatment, as spontaneous remissions have also been observed in patients with FAP whom which an active surveillance could also be a valid therapeutic option. The particularity of desmoids tumors

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]

associated to PAF lies in their predominantly intra-abdominal location and the risk of complication. In the last ten years, surgery has largely given way to conservative treatments such as chemotherapy and more recently to tyrosine kinase inhibitors that have shown their efficacy with a significant improvement in progression-free survival of patients."

Yogesh Kumar, B., Vidyachara, S. & Vadhiraja, B.M. 2019.
"Aggressive fibromatosis is a benign, locally invasive fibroblastic proliferation that can cause compressive effects on adjacent structures. The primary cure of this disease rests in wide excision of the tumor. Unfortunately even when surgical margins are clear of tumor, recurrence rates are high. Postoperative radiotherapy is indicated following surgical excision. We present a 13-year-old girl who had been operated for the intraspinal mass in upper thoracic spine and paraparesis with thoracic limited laminectomy and excision of the tumor mass elsewhere. The histopathological examination was reported to be aggressive fibromatosis. After 2 years, she presented again with 1-year duration of progressive deformity in the upper thoracic spine and weakness of both lower limbs. Focal kyphosis at T4-T5 was measuring 68°. Magnetic resonance imaging (MRI) showed recurrent tumor involvement of posterior elements of T2-T5 and paravertebral soft tissues with signal changes in the cord at T2-T5 vertebral levels with focal kyphosis and internal gibbus. She underwent posterior spinal revision decompression with internal gibbectomy and instrumented fusion. The histopathology showed features suggestive of aggressive fibromatosis. After wound healing at 2 weeks, she underwent 3-D conformal radiotherapy, based on the preoperative tumor extent on MRI (dose of 45 Gy in 25 fractions over 5 weeks). She had normal neurology at 2-year follow-up and was tumor free on MRI. Hence, aggressive fibromatosis can recur following successful surgical wide excision. Multilevel thoracic laminectomy in growing children can cause progressive spinal deformity and neurological deficits. Operative treatment of recurrent tumor involves en bloc excision with instrumented fusion followed by local radiotherapy. This is the first pediatric recurrent spinal fibromatosis reported with successful treatment as per author's knowledge."

Desai, S.R., Dombale, V.D. & Janugade, H.B. 2005.
Infantile fibromatosis represents the childhood counter part of musculoaponeurotic fibromatosis & arises as a solitary mass in skeletal muscle, adjacent fascia, aponeurosis or periosteum. The lesion is extremely rare. Microscopically it exists in two forms diffuse (mesenchymal) & desmoid. The less common desmoid form rarely occurs in infancy. Immunophenotype shows vimentin positivity with variable positivity with muscle markers. The differential diagnosis of this type is infantile fibrosarcoma. The tumor may locally recur if inadequately excised. We report a case of infantile fibromatosis of desmoid type occurring in 10 months male child for its extreme rarity.

Incidence of Childhood Desmoid Tumour.
The National Cancer Registry (2016) does not provide any information on the incidence of childhood desmoid tumour.

Childhood desmoid tumour represents one of the rarer types of childhood tumours. They occur in children and young adults and arise from muscle or connective tissue ('soft tissue') around muscles or bones, and can appear anywhere in the body. They can also occur at any time throughout childhood.

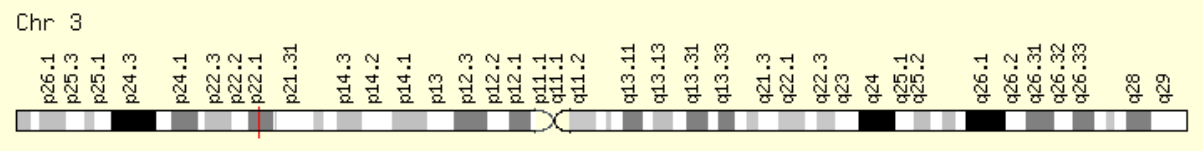
Desmoid tumours are neither a truly benign nor a truly malignant cancer. It can be life-threatening if located next to vital organs like the spine or trachea (windpipe). Surgical removal of the entire tumour usually achieves a cure, however, if even small amounts of tumour cells remain, the tumour can grow

back again. Depending on the location of the tumour, surgical removal may not be possible. In these cases, radiation therapy or chemotherapy may prevent further tumour growth or cause the tumour to disappear.

Causes of Childhood Desmoid Tumour

The cause of desmoid tumours is unknown.

In some patients, desmoid tumours can occur as part of an inherited syndrome called Gardner Syndrome, in which patients also have colon polyps or colon cancer. Desmoid tumours can also occur in pregnant women, which has led to the theory that hormones may influence growth. Most of the time, desmoid tumours occur in previously healthy patients with no other medical problems.

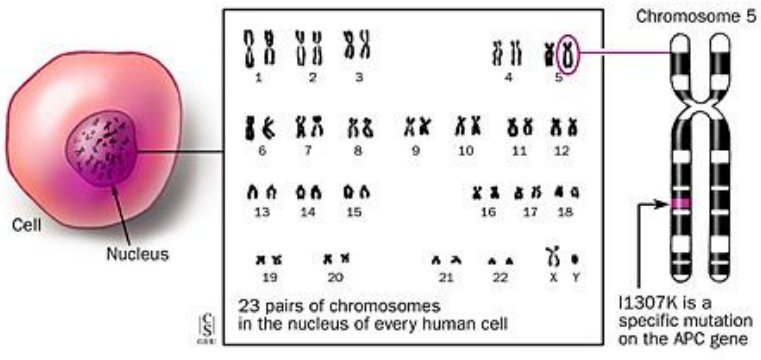


[Picture Credit: CTNNB1 Gene]

Mutations in the *CTNNB1* gene or the *APC* gene cause desmoid tumours. *CTNNB1* gene mutations account for around 85 percent of sporadic desmoid tumours. *APC* gene mutations cause desmoid tumours associated with familial adenomatous polyposis as well as 10 to 15 percent of sporadic desmoid tumours. Both genes are involved in an important cell signalling pathway that controls the growth and division (proliferation) of cells and the process by which cells mature to carry out specific functions (differentiation).

The *CTNNB1* gene provides instructions for making a protein called beta-catenin. As part of the cell-signalling pathway, beta-catenin interacts with other proteins to control the activity (expression) of particular genes, which helps promote cell proliferation and differentiation. *CTNNB1* gene mutations lead to an abnormally stable beta-catenin protein that is not broken down when it is no longer needed. The protein accumulates in cells, where it continues to function in an uncontrolled way.

[Picture Credit: APC Gene on Chromosome 5]



The protein produced from the *APC* gene helps regulate levels of beta-catenin in the cell. When beta-catenin is no longer needed, the APC protein attaches (binds) to it, which signals for it to be broken down. Mutations in the *APC* gene that cause desmoid tumours lead to a short APC protein that is unable to interact with beta-catenin. As a result, beta-catenin is not broken down and, instead, accumulates in cells. Excess beta-catenin, whether caused by *CTNNB1* or *APC* gene mutations, promotes uncontrolled growth and division of cells, allowing the formation of desmoid tumours.

Signs and Symptoms of Childhood Desmoid Tumour
The most common symptom of desmoid tumours is pain. Other signs and symptoms, which are often caused by growth of the tumour into surrounding tissue, vary based on the size and location of the tumour. Intra-abdominal desmoid tumours can block the bowel, causing constipation. Extra-abdominal desmoid tumours can restrict the movement of affected joints and cause limping or difficulty moving the arms or legs.

Desmoid tumours occur frequently in people with an inherited form of colon cancer called familial adenomatous polyposis (FAP). These individuals typically develop intra-abdominal desmoid tumours in addition to abnormal growths (called polyps) and cancerous tumours in the colon. Desmoid tumours that are not part of an inherited condition are described as sporadic (Genetics Home Reference).

Diagnosis of Childhood Desmoid Tumour
CT scanning and MRI are used for the diagnosis and follow-up of desmoid tumours. They can help determine the extent of the tumour and its relationship to nearby structures, especially prior to surgical removal. MRI is superior to CT scanning in defining the pattern and the extent of involvement as well as in determining if recurrence has occurred after surgery.

The preferred diagnostic test is biopsy of the tumour. A fine-needle aspiration biopsy specimen may be considered.

Electron microscopy may be performed. On electron microscopic examination, the spindle cells of desmoid tumours appear to be myofibroblasts. This finding is thought to represent an abnormal proliferation of myofibroblasts, which normally disappear gradually during the later stages of wound healing.

Bonvalot, S., Tzanis, D. & Bouhadiba, T. 2020.
"After an adapted imaging, the diagnosis of a desmoid tumor (DT) is provided by a percutaneous microbiopsy, with a molecular analysis for beta-catenin or APC gene mutation. The therapeutic strategy must be decided in a specialized multidisciplinary tumor board (MTB). Surgery is no longer the first-line treatment for a DT. Except within a surgical complication, active surveillance is offered to the majority of patients, since more than half stabilize or regress after an initial progression, whether the location is peripheral or intra-abdominal. If the localization and/or volume are likely to be functional or life-threatening, medical induction therapy is discussed in MTB, before a local treatment whose potential sequelae would be definitive. Incomplete unplanned resection, recurrence, pregnancy or desmoids occurring in a polyposis context are no longer routine surgical indications. In an emergency setting (occlusion, peritonitis), it is discussed to treat only the mechanical complication and leave the DT in place, if its resection would lead to too much digestive resection, especially in patients who have already undergone colectomy for polyposis. The best indications for surgery are patients who have parietal locations with significant and documented progression, because surgery can be easily completed at the cost of an acceptable morbidity. In localizations where surgery would cause sequelae, medical treatment or other regional loco treatments are discussed in MTB."

Malik, F., Wang, L., Yu, Z., Edelman, M.C., Miles, L., Clay, M.R., Hedges, D., Brennan, R.C., Nichols, K.E., McCarville, M.B. & Bahrami, A. 2020.

Aims: Several morphologically overlapping (myo)fibroblastic neoplasms harbour USP6 fusions, including aneurysmal bone cysts, nodular fasciitis, myositis ossificans, cranial fasciitis, fibro-osseous pseudotumour of the digits, and cellular fibroma of the tendon sheath. USP6-induced neoplasms are almost universally benign and cured by local excision. We aim to highlight the diagnostic value of USP6 fusion detection in a series of aggressive-appearing paediatric myofibroblastic tumours.

Methods and results: Three deep-seated, radiographically aggressive, and rapidly growing childhood myofibroblastic neoplasms were morphologically and molecularly characterised by USP6 break-apart fluorescence in-situ hybridisation (FISH), transcriptome sequencing, and targeted capture analysis. Each tumour occurred in the lower-extremity deep soft tissue of a child presenting with pain, limping, or a mass. In all three patients, imaging studies showed a solid mass that infiltrated into surrounding skeletal muscle or involved/eroded underlying bone. The biopsied tumours consisted of variably cellular myofibroblastic proliferations with variable mitotic activity that lacked overt malignant cytological features. FISH showed that all tumours had USP6 rearrangements. On the basis of these results, all three patients were treated with conservative excision with positive margins. The excised tumours had foci resembling nodular fasciitis, fibromatosis, and pseudosarcomatous proliferation. Next-generation sequencing revealed COL1A1-USP6 fusions in two tumours and a COL3A1-USP6 fusion in the third tumour. One tumour had a subclonal somatic APC in-frame deletion. No recurrence was observed during follow-up (8-40 months).

Conclusion: We present a series of benign, but aggressive-appearing, USP6-rearranged myofibroblastic tumours. These deep-seated tumours had concerning clinical and radiographic presentations and did not fit into one distinct histological category. These cases highlight the diagnostic value of USP6 fusion detection to identify benign nondescript tumours of this group, especially those with aggressive features, to avoid overtreatment.

Treatment Options

Primary surgery with negative surgical margins is the most successful primary treatment modality for desmoid tumours. Positive margins after surgery reflect a high risk for recurrence.

In those patients who refuse surgery or are not surgical candidates the following options may be considered:

- Radiation therapy may be used as a treatment for recurrent disease or as primary therapy to avoid mutilating surgical resection. It may be used postoperatively, preoperatively, or as the sole treatment.
- Pharmacologic therapy with anti-oestrogens and prostaglandin inhibitors may also be used.
- In cases of recurrent extra-abdominal desmoid tumours in which surgery is contraindicated or in cases of recurrence, a chemotherapeutic regimen of doxorubicin, dacarbazine, and carboplatin may be effective. Intra-abdominal desmoid tumours as a part of Gardener syndrome may respond to systemic doxorubicin, and ifosfamide can be useful for patients with complications from the tumour. Polychemotherapy has been used and can be combined with targeted therapy with imatinib.

- Expanded knowledge of familial adenomatosis polyposis–desmoid tumour molecular underpinnings may aid in the development of novel therapeutic strategies.

Excision of tumour - aggressive, wide surgical resection is the treatment of choice. Complete surgical excision of desmoid tumours is the most effective method of cure. This sometimes necessitates removal of most of an anterior compartment of a leg. Extensive cases may require excision plus adjuvant treatment including chemotherapy and repeat surgery. In selected patients, radical resection with intraoperative margin evaluation by frozen sections followed by immediate mesh reconstruction may be a safe and effective procedure providing definitive cure yet minimizing functional limitations.

For tumours that are asymptomatic or non-progressive, some prefer a wait-and-see approach.

The goals of pharmacotherapy are to induce remission, to prevent complications, and to reduce morbidity. Local recurrences are frequent after surgery, particularly if margins are positive. Radiotherapy alone for gross disease or after a microscopically incomplete resection yields local control rates of approximately 75-80%.

The following agents inhibit cell growth and proliferation. Pharmacologic agents result in objective response rates of approximately 40-50%; the duration of response is variable.

Doxorubicin (Adriamycin, Rubex)

Inhibits topoisomerase II and produces free radicals, which may cause the destruction of DNA. The combination of these 2 events can, in turn, inhibit the growth of neoplastic cells.

Dacarbazine (DTIC-Dome)

Inhibits DNA, RNA, and protein synthesis. Inhibits cell replication throughout all phases of the cell cycle.

Carboplatin (Paraplatin)

Analog of cisplatin. Has same efficacy as cisplatin but with better toxicity profile.

Kasper, B., Raut, C.P. & Gronchi, A. 2020.
"Desmoid tumors (DTs) are a rare disease of intermediate malignancy characterized histologically by a locally aggressive, monoclonal, fibroblastic proliferation and clinically by a variable and often unpredictable course. For decades, surgical resection has been the standard initial treatment approach; however, more recently, a paradigm shift toward a more conservative treatment strategy has been introduced. More than 5 years ago, The Desmoid Tumor Working Group started a consensus initiative in Europe with the aim of harmonizing the strategy among clinicians and setting up treatment recommendations for patients with DTs. This review summarizes the latest joint, global, evidence-based guideline approach to DT management. Moreover, a number of gray areas in the treatment recommendations are discussed, and possible future perspectives on the treatment armamentarium for patients with DTs are presented."

Sanchez-Mete, L., Ferraresi, V., Caterino, M., Martayan, A., Terrenato, I., Mannisi, E. & Stigliano, V. 2020.
(1) Background: desmoid tumors (DTs) are common in patients with familial adenomatous polyposis (FAP). An active surveillance approach has been recently proposed as a valuable alternative to immediate treatment in some patients. However, no clear indication exists on which patients are

suitable for active surveillance, how to establish the cut-off for an active treatment, and which imaging technique or predictive factors should be used during the surveillance period.
(2) Results: we retrospectively analyzed 13 FAP patients with DTs. A surveillance protocol consisting of scheduled follow-up evaluations depending on tumor location and tissue thickening, abdominal computed tomography (CT) scan/Magnetic resonance imaging (MRI) allowed prompt intervention in 3/11 aggressive intra-abdominal DTs, while sparing further interventions in the remaining cases, despite worrisome features detected in three patients. Moreover, we identified a possible predictive marker of tumor aggressiveness, i.e., the "average monthly growth rate" (AMGR), which could distinguish patients with very aggressive/life-threatening tumor behavior (AMGR > 0.5) who need immediate active treatment, from those with stable DTs (AMGR < 0.1) in whom follow-up assessments could be delayed. (3) Conclusion: surveillance protocols may be a useful approach for DTs. Further studies on larger series are needed to confirm the usefulness of periodic CT scan/MRI and the value of AMGR as a prognostic tool to guide treatment strategies.

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

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/

Medical Disclaimer
This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst CANSA has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted or Utilised

APC Gene on Chromosome 5
https://www.google.co.za/search?q=apc+tumor+suppressor+gene&source=lnms&tbm=isch&sa=X&ei=vtHkU9afLbGS7Abki4GQDQ&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=wCXWAnFG_wqZaM%3A%3B2AR3AsaDuXvR_M%3BwCXWAnFG_wqZaM%3A&imgrc=wCXWAnFG_wqZaM%253A%3BcCG-3l-kkPMAqM%3Bhttp%253A%252F%252Fghr.nlm.nih.gov%252FdynamicImages%252Fchromomap%252FAPC.jpeg%3Bhttp%253A%252F%252Fghr.nlm.nih.gov%252Fgene%252FAPC%3B469%3B175

Bonvalot, S., Tzanis, D. & Bouhadiba, T. 2020. Desmoid tumors: are there still any surgical indications? *Bull Cancer*. 2020 Mar;107(3):364-370.

Buitendijk, S., van de Ven, C.P., Dumans, T.G., den Hollander, J.C., Nowak, P.J., Tissing, W.J., Pieters, R. & van den Heuvel-Eibrink, M.M. 2005. Pediatric aggressive fibromatosis: a retrospective analysis of 13 patients and review of literature. *Cancer*. 2005 Sep 1;104(5):1090-9. Review.

Childhood Desmoid Tumour
https://www.google.co.za/search?q=childhood+desmoid+tumor&source=lnms&tbm=isch&sa=X&ei=_ovkU8aIGOOv7AbL4oHQAQ&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=Dn8NSyFl2zX4ZM%253A%3BR2vAiiBmr7cJMM%3Bhttp%253A%252F%252Fwww.eplasty.com%252Farticle_images%252Feplasty09e52_fig1.gif%3Bhttp%253A%252F%252Fwww.eplasty.com%252Findex.php%253Foption%253Dcom_content%2526id%253D357%2526catid%253D170%253Avolume-09-eplasty-2009%2526Itemid%253D121%3B640%3B853

CTNNB1
https://www.google.co.za/search?q=ctnnb1+gene&source=lnms&tbm=isch&sa=X&ei=M9DkU_H5Ba-w7AaqtoDwCA&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=714&dpr=0.9#facrc=_&imgdii=_&imgrc=ldUm95XwRVBigM%253A%3B4b37FFccCs1GeM%3Bhttp%253A%252F%252Fwww.genecards.org%252Fpics%252Floc%252FCTNNB1-gene.png%3Bhttp%253A%252F%252Fwww.genecards.org%252Fcgi-bin%252Fcarddisp.pl%253Fgene%253DCTNNB1%3B720%3B90

Dana-Farber Cancer Institute
http://www.dana-farber.org/Health-Library/Childhood-Desmoid-Tumor.aspx

Desai, S.R., Dombale, V.D. & Janugade, H.B. 2005. Infantile firobatosis (desmoid type) a case report. *Indian J Pathol Microbiol*. 2005 Jul;48(3):379-80.

Genetics Home Reference
http://ghr.nlm.nih.gov/condition/desmoid-tumor

Kasper, B., Raut, C.P. & Gronchi, A. 2020. Desmoid tumors: to treat or not to treat, that is the question. *Cancer*. 2020 Dec 15;126(24):5213-5221.

Malik, F., Wang, L., Yu, Z., Edelman, M.C., Miles, L., Clay, M.R., Hedges, D., Brennan, R.C., Nichols, K.E., McCarville, M.B. & Bahrami, A. 2020. Benign infiltrative myofibroblastic neoplasms of childhood with USP6 gene rearrangement. *Histopathology*. 2020 Nov;77(5):760-768.

Medscape
http://emedicine.medscape.com/article/1060887-workup#a0720
http://emedicine.medscape.com/article/1060887-treatment
http://emedicine.medscape.com/article/1060887-treatment#a1156
http://emedicine.medscape.com/article/1060887-medication
http://emedicine.medscape.com/article/1060887-medication#2

National Cancer Institute
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

Sanchez-Mete, L., Ferraresi, V., Caterino, M., Martayan, A., Terrenato, I., Mannisi, E. & Stigliano, V. 2020. Desmoid Tumors Characteristics, Clinical Management, Active Surveillance, and Description of Our FAP Case Series. J Clin Med. 2020 Dec 11;9(12):4012.

St Jude Children's Research Hospital
http://www.stjude.org/stjude/v/index.jsp?vgnextoid=459d061585f70110VgnVCM1000001e0215acRCRD

Tayeb Tayeb, C., Parc, Y., Andre, T. &, Lopez-Trabada Ataz, D. 2020. Familial adenomatous polyposis, desmoid tumors and Gardner syndrome. *Bull Cancer*. 2020 Mar;107(3):352-358.

Yogesh Kumar, B., Vidyachara, S. & Vadhiraja, B.M. 2019. Pediatric recurrent aggressive spinal gibromatosis with progressive kyphosis and neurological deficits. *J Orthop Surg (hong Kong).* 2019 May-Aug;27(2):2309499019846618. doi: 10.1177/2309499019846618.