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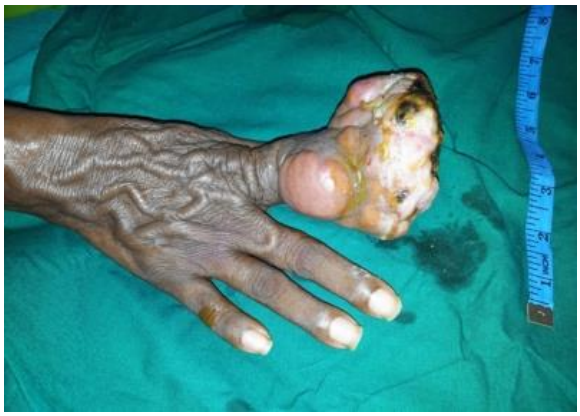
Fact Sheet on Desmoid Fibromatosis

Introduction



[Picture Credit: Desmoid Fibromatosis]

Desmoid tumours (fibromatosis) are tumours that arise from cells called fibroblasts. Fibroblasts are found throughout the body and their main function is to provide structural support and protection to the vital organs such as lung, liver, blood vessels, heart, kidneys, skin, and intestines. They also play a critical role in wound healing.

When fibroblast cells undergo mutations they can become Desmoid tumours (also known as "aggressive fibromatosis"). Desmoid tumours can arise in virtually any part of the body. These tumours often occur in women in their 30's, but can occur in anyone at any age. Desmoid tumours can be slow growing or extremely aggressive. They do not metastasise (move from one body part to another), and if slow growing they can be carefully watched by one's physician. However, when they are aggressive they can cause life threatening problems or even death when they compress vital organs such as intestines, kidney, lungs, blood vessels, and nerves.
(Desmoid Tumor Research Foundation).

Desmoid Fibromatosis

Desmoid fibromatosis, also called Desmoid tumours, are rare benign (non-cancerous) fibrous growths that occur rarely in the general population (5 to 6 per 1 million per year) but frequently in one of the familial cancer predisposition conditions known as familial adenomatous polyposis (FAP) or Gardner syndrome, affecting between 3.6% and 20% of patients. About 2% of all Desmoid tumours arise in patients with FAP. Desmoid tumours may occur in any musculoaponeurotic tissue structures of the body, although they tend to be in extremities and spinal areas in the general population and in the abdomen in FAP.

Other synonyms of Desmoid Fibromatosis:

- aggressive fibromatosis
- deep fibromatosis
- musculoaponeurotic fibromatosis

- nonmetastasising fibrosarcoma
- grade I fibrosarcoma

Desmoid tumours are not considered sarcomas; however, they have been classified as 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.

The optimal treatment plan usually requires multidisciplinary teams only found in sarcoma centres. Surgeons with expertise in sarcomas should guide the approach to extra-abdominal lesions, while intra-abdominal Desmoids are best considered by teams including sarcoma surgeons together with GI surgeons, oncologists and radiation therapists all with Desmoid tumour experience and expertise.

Desmoid tumours do not metastasise but may infiltrate adjacent structures, extend along fascial planes, attach to and erode bones, and engulf and compress blood vessels, nerves, ureters, and other hollow organs of the abdomen. Severe and even fatal clinical problems are sometimes caused by these tumours, especially if mesenteric vessels or other abdominal organs are obstructed. Other complications include bowel perforation, fistulisation, bleeding and ureteral obstruction. Desmoid tumours usually enlarge very gradually and sometimes stop growing altogether. Only about one third of abdominal Desmoid tumours cause pain, although the most common symptom is abdominal pain. Intra-abdominal Desmoid tumours sometimes become massive, occupying much of the abdominal cavity and encasing many segments of viscera.
(The Liddy Shriver Sarcoma Initiative; National Organization for Rare Diseases).

Incidence of Desmoid Fibromatosis in South Africa
Because Desmoid Fibromatosis is not a cancerous condition, the South African National Cancer Registry (2010) does not provide any information regarding its incidence.

Signs and Symptoms of Desmoid Fibromatosis
The exact cause of Desmoid tumour still remains unknown. Desmoid tumours may present sporadically or as a manifestation of a hereditary syndrome called familial adenomatous polyposis (FAP). FAP is a familial cancer predisposition syndrome which, if left untreated at an early age, almost always results in colorectal cancer. Up to 32% of FAP patients will develop Desmoid tumours in their lifetime. These Desmoid tumours are the result of mutations, or changes, in a gene called adenomatous polyposis coli (APC).

For most affected individuals, Desmoid tumours occur in a sporadic manner, meaning that they are not caused by a predisposing genetic disease. People who develop Desmoid tumours in a sporadic manner have no other health problems associated with mutations in the APC gene and have no close family members with the tumours. Repeated irritation or trauma to a certain part of the body, including surgical trauma, has been theorised to increase the risk of Desmoid tumour occurrence. Oestrogen also seems to play a role in the development of Desmoid tumours.

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 or muscles
- Pain and obstruction of the bowels
- Limping or other difficulty using affected legs, feet, arms or hands or other affected part of the body

(National Organization for Rare Diseases; Desmoid Tumor Research Foundation).

Diagnosis of Desmoid Fibromatosis

Desmoid tumours are cytologically bland fibrous neoplasms originating from the musculoaponeurotic structures throughout the body. The term desmoid, coined by Muller in 1838, is derived from the Greek word *desmos,* which means tendonlike.

Desmoid tumors often appear as infiltrative, usually well-differentiated, firm overgrowths of fibrous tissue, and they are locally aggressive. The synonym aggressive fibromatosis describes the marked cellularity and aggressive local behaviour. This course and the tendency for recurrence make the treatment of these relatively rare fibrous tumours challenging.

The differential diagnosis of Desmoid-type fibromatosis is broad, with fibroblastic sarcomas on the one extreme and reactive fibroblastic and myofibroblastic processes such as nodular fasciitis and even hypertrophic scars and keloids on the other. Different considerations apply for extra-abdominal and abdominal fibromatosis. Fortunately, nuclear staining for β-catenin greatly aids in the diagnosis and is a consistent finding (approximately 80% of cases), although it is not specific and is also seen in a rather large variety of other tumours. The diagnosis can be confirmed by screening for mutations (mainly in exon 3) of the β-catenin gene, which are found in ~85% of sporadic cases.
(The Oncologist).

Treatment Options for Desmoid Fibromatosis

Treatment of Desmoid Fibromatosis includes:

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.

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 minimising functional limitations.

Evidence suggests that pregnancy does not adversely affect surgical outcomes.

Lesions involving the extremities and deep soft tissues of the trunk have a higher risk of recurrence, as do Gardner syndrome–associated lesions in other locations.

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

In those patients who refuse surgery or are not surgical candidates, the options below 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 Gardner 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.
(Medscape).

Radiation therapy – this has been incorporated into the management of extra-abdominal fibromatosis, either as an adjuvant treatment to surgical resection in cases of positive surgical margins or as a primary treatment when surgical resection is not feasible or may result in significant loss of function. Many studies support its efficacy. However, direct tissue toxicity and potential late radiation effects, including second malignancies, are important considerations in the treatment of otherwise healthy, often, young patients. The use of radiotherapy in children with AF should, therefore, be highly limited.
(Bonvalot, *et al*.)

Medical treatment – medical treatment usually comes to the forefront when surgery and radiation cannot be used or have failed. Occasionally, however, systemic therapy is given before surgery to shrink large, potentially resectable Desmoid tumours that would otherwise incur excessive surgery-related morbidity in patients for whom radiation therapy would be inappropriate—for example, in patients with a Desmoid tumour deep in the pelvis or abdomen, sites prone to high radiation toxicity. Medical therapy for Desmoid tumours usually involves individualised combinations of antihormone agents, typically tamoxifen or raloxifene; nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen; targeted chemotherapy with imatinib mesylate; and/or traditional cytotoxic chemotherapy.
(MD Anderson Cancer Center).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may

also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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