Desmoid tumors: diagnostic and therapeutic considerations

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Abstract

A literature review on desmoid tumors was carried out, which are tumors that affect soft tissues with a locally aggressive behavior and are unable to metastasize. Sporadic cases are located on the extremities and chest wall; hereditary cases have an intra-abdominal predilection, and those associated with pregnancy occur on the abdominal wall. Imaging techniques assess disease extension. Trucut biopsy is the study of choice for diagnosis. Mutations in the CTNNB1 or APC genes cause an abnormal accumulation of β -catenin within the cell. In this review, an emphasis is made on therapeutic strategies' evolution and change, and current tools for decision making are analyzed, as well as clinical outcomes. Radiation therapy can play a therapeutic or adjuvant role. Advances in the understanding of the disease have allowed establishing better targeted treatments with lower morbidity; however, there are still unanswered questions regarding the choice of the ideal candidate for surveillance and/or early treatment. Data related to quality of life are also presented, as well as the uncertainty generated by this diagnosis for both doctor and patient.

KEY WORDS: Desmoid tumor. Aggressive fibromatosis. β -catenin. Sarcoma.

Tumores desmoides: consideraciones diagnóstico-terapéuticas

Resumen

Se realizó una revisión bibliográfica de los tumores desmoides, lo cuales afectan los tejidos blandos con un comportamiento localmente agresivo sin capacidad de producir metástasis. Los casos esporádicos se localizan en extremidades y pared torácica; los casos hereditarios tienen predilección intraabdominal y los asociados con el embarazo en la pared abdominal. Las técnicas de imagen evalúan la extensión de la enfermedad. La biopsia con aguja trucut es el estudio de elección para el diagnóstico. Las mutaciones en el gen CTNNB1 o en el gen de APC provocan acumulación anormal de betacatenina en la célula. En esta revisión se hace énfasis en la evolución y cambio de las estrategias terapéuticas y se analizan las actuales herramientas para la toma de decisiones, así como los resultados clínicos. La radioterapia puede tener un papel terapéutico o adyuvante. Los avances en la comprensión de la enfermedad han permitido establecer tratamientos mejor dirigidos y con menor morbilidad; sin embargo, aún existen interrogantes en cuanto a la elección del candidato ideal para la vigilancia o el tratamiento precoz. También se presentan datos relacionados con la calidad de vida y la incertidumbre que genera el diagnóstico en el médico y el paciente.

PALABRAS CLAVE: Tumor desmoide. Fibromatosis agresiva. Betacatenina. Sarcoma.

Introduction

Desmoid tumors belong to an entity known as fibromatosis, which includes tumors that affect soft tissues and is divided into superficial and deep. The

superficial type includes the palmar, plantar and penile variants, also known as Dupuytren's contracture, Ledderhose disease and Peyroni's disease, respectively. Deep fibromatosis represents a single entity also known as aggressive fibromatosis, desmoid fibromatosis or

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desmoid tumors.¹ According to the World Health Organization, desmoid tumors belong to the group of fibroblastic/myofibroblastic tumors of intermediate or locally aggressive behavior, are clonal fibroblastic proliferations that originate in deep soft tissues and are characterized by infiltrative growth and a tendency towards local recurrence, with no capacity to generate metastasis.²

The purpose of the present article was to carry out a literature review on desmoid tumors and their treatment, with an emphasis on the evolution of therapeutic strategies, as well as to analyze the tools for decision-making and clinical results.

Epidemiology

Desmoid tumors account for 0.03 % of all neoplasms and 3 % of soft tissue tumors.³ They have a peak incidence at between the third and fourth decades of life and are more common in women (2:1).⁴ Most are sporadic in nature, and between 5 and 15 % of cases have a hereditary form associated with familial adenomatous polyposis syndrome and its variant, Gardner syndrome. Sporadic cases occur mainly in the extremities, chest wall, head, neck and breast. The group associated with pregnancy is mainly located in the abdominal wall.⁵ Other associated risk factors include pregnancy, hormone treatments, surgeries or previous trauma.^{6,7}

Diagnosis

Clinical

Manifestations can be variable, ranging from asymptomatic presentations to incapacitating functional limitations. The main symptom is volume augmentation. In the extremities, tumors are associated with pain, paresthesia, neuropathies or functional limitations when they generate neurovascular compression; in the head and neck, they are associated with dyspnea or stridor; abdominal presentations can occur with intestinal obstruction, ulceration, bleeding, ischemia and even perforations.⁸⁻¹⁰

Radiological

Ultrasound, computed axial tomography and magnetic resonance imaging are the main diagnostic tools. Tissue appearance is variable depending on its

fibrotic, vascular or cellular composition, according to the stage.¹¹ Ultrasound is usually the initial study, especially in patients with tumors in extremities or abdominal wall, and is the study of choice for follow-up and guided biopsies; the image shows an oval mass with smooth contour or a poorly-defined soft tissue tumor with variable echogenicity, with hypo- and hyperechoic areas, which are correlated with histological composition.¹² The “tail sign” indicates a linear extension in the fascial planes and the “staghorn sign” is attributed to finger-like intramuscular projections of the tumor.¹³ On computed axial tomography scan, well-delimited soft tissue lesions (such as in the abdominal wall) or infiltrative margins (mesentery) can be observed; it is the study of choice for monitoring intra-abdominal tumors.¹⁴ Magnetic resonance imaging is the study of choice for extra-abdominal presentations and in subjects who are allergic to iodine-containing contrast medium. The “band sign” (linear bands within the tumor that show no enhancement with contrast medium, hypointense in T1 and T2) represents a characteristic finding (observed in 60 to 90 % of patients).^{15,16} Intramuscular tumors show a fatty tissue border surrounding them (“split fat sign”) or flame-shaped margins (“flame sign”).^{17,18}

Histopathology

Performing a biopsy with a 14-16 G Tru-cut needle is recommended; the samples should be examined by a pathologist expert in soft tissue tumors, otherwise, up to 30 to 40 % of cases can be incorrectly diagnosed.¹⁹ On gross examination, desmoid tumors are firm, gray or whitish masses and sometimes they resemble scar tissue.¹⁷ Microscopically, they are heterogeneous, poorly delimited, with uniform proliferation of spindle cells that resemble myofibroblasts within a stroma with abundant collagen and a vascular network lacking capsule.²⁰ There is no atypia, necrosis or mitosis. On immunohistochemistry they are nuclear, positive for β -catenin, vimentin, COX2, tyrosine kinase, PDGFRb, androgen and beta estrogen receptors, and negative for desmin, S-100, h-caldesmon, CD34 and CKIT.²¹⁻²⁴ Knowledge of molecular biology and cytogenetics might contribute to the selection of individualized treatment in the future.

Treatment

The management of patients with desmoid tumors requires a careful evaluation of each case and its

Table 1. Systemic treatment options in adults with desmoid tumors: “best available evidence”*

Treatment	Type of study	n	Objective response	Other conclusions	Reference**
Sulindac	Retrospective	14	57 %		38
Toremifene	Retrospective	27	22 %	6-month PFS: 76 %	39
Methotrexate-vinblastine	Phase II	27	15 %	10-year PFS: 67 %	40
Pegylated liposomal doxorubicin	Retrospective	14	33 %		41
Doxorubicin + dacarbazine	Retrospective	12	50 %		42
Imatinib 800 mg/day	Phase II	51	6 %	1-year PFS: 66 %	43
Imatinib 800 mg/day	Phase II	37	3 %	6-month PFS: 65 %	44
Imatinib 400 mg/day	Phase II	50	12 %	1-year PFS: 67 %	45
Sunitinib	Phase II	19	26 %	1-year PFS: 80 %	46
Sorafenib	Retrospective	26	26 %		21

*Table obtained from Penel N, Chibon F, Salas S. Adult desmoid tumors: biology, management and ongoing trials.³⁴

**References are those indicated in the original article.

PFS = progression-free survival.

variables, as well as direct communication with the patient.

Active surveillance

Until a few years ago, surgery was the treatment of choice; currently, starting with a period of active surveillance is recommended.^{19,25} Approximately 50 % of cases stabilize in 14 to 19 months, and 25 % show tumor regression, which indicates that active surveillance is a safe strategy. When there is progression, it usually appears within the first months and it is hardly observed after three years on follow-up; only 14 to 16 % of cases will require surgical treatment.²⁶⁻²⁹ Active surveillance should include close follow-up with magnetic resonance imaging or computed axial tomography every month during the first two months, every three months during the first year, every six months until the fifth year, and then annually.

Systemic treatment

It is implemented in patients with progression during the active surveillance period (excluding those with tumors on the abdominal wall) or in patients who reject this option. Anti-inflammatory drugs, estrogen blockers, targeted therapies, and even combined chemotherapy regimens can be used. Most commonly used anti-inflammatory drugs include sulindac, indomethacin, meloxicam and celecoxib; in addition to

generating an improvement in pain, they can block the β -catenin pathway through COX2, or prostaglandin pathway, and thereby induce response.^{30,31}

The most widely used hormonal agents are tamoxifen and toremifene, alone or in combination with anti-COX2 anti-inflammatory drugs; these drugs are usually the first line of treatment due to their good tolerance and low toxicity. Doses of 20 to 80 mg/day of tamoxifen and 60 to 180 mg/day of toremifene have been used. The exact mechanism of action of these drugs in this pathology is unknown.³² Chemotherapy treatment is considered the first option in patients with rapid progression or advanced disease and unresectable tumors. Anthracycline-based regimens demonstrate high response rates, as well as the combination of methotrexate with vinorelbine or vinblastine, and is considered a first-line treatment. Tyrosine kinase inhibitors have been successfully used; even when the specific site of action is not known, they inhibit cell growth and proliferation.³³ Finally, sorafenib might be useful in the treatment of patients with progressive, symptomatic disease or patients with unresectable tumors or that require considerably extensive resections that compromise the function, since an objective response of 33 % was observed in a group that received sorafenib in comparison with 20 % in the placebo group, as well as a 2-year progression-free interval of 81 % in contrast with 36 % in the placebo group.³⁴ The evidence on systemic treatments in adults is shown in table 1.

Surgical Treatment

The elevated recurrence rate (from 25 to 60 % at five years), as well as the need for extensive (and sometimes disabling) surgeries, has led to an evolution in the treatment of these patients, with surgery being reserved for a minority of subjects.³⁵

Understanding of the behavior of these tumors has focused on identifying individual prognostic factors that determine whether more invasive strategies are required since the beginning of treatment, and on identifying those individuals who can really benefit from surgery. One of the studied factors has been tumor location; those occurring in the extremities have the poorest prognosis when treated with surgery, with recurrence rates of up to 60 %, unlike 17 to 30 % for other locations.³⁶⁻³⁸ When surgical treatment is necessary, current recommendation is to choose function-preserving procedures, even when positive microscopic margins are left, and only when other treatments have failed to stabilize or control the disease.³⁹

Unlike other sarcomas, microscopically positive surgical margin in desmoid tumors is not consistently related to an increase in local relapses. Although some studies have identified this as an adverse factor, recording this result in all series has not been possible, probably because they are retrospective, heterogeneous and with variable management of the pathology specimens, in addition to the characteristics inherent to this disease. Resection with negative margin should be considered as long as it does not generate significant limitation.^{26,35,36}

Another prognostic factor that has been studied is gender: the male gender has been considered to be an adverse factor despite the higher frequency of desmoid tumors in women (generally, desmoid tumors in the abdominal wall and with a better prognosis *per se*, as well as with a higher probability of tumor regression and that require surgical procedures with less functional impact).^{40,41} In the multivariate analysis results, only patient age, tumor location and tumor size were factors related to an increase in postoperative recurrences. All these factors can be determined since the diagnostic stage and are helpful for formulating recommendations.⁴²

According to the latest European consensus on desmoid tumors, surgery should be an option in cases of progression despite medical treatment or radiotherapy, always considering location and age. On rare occasions, amputations are performed due to desmoid tumors, which are an option only when unresectable recurrences occur with limb-sparing surgeries, or when they are

symptomatic and disabling, or when treatment-derived secondary effects (surgery with or without radiotherapy) generate significant loss of function or disabling chronic symptoms.⁴⁰ Finally, mesenteric or retroperitoneal tumors not associated with familial polyposis can be treated since the beginning with surgery, due to the morbidity they can generate, their size and related symptoms.

Radiotherapy

The recommendation for its use in the Italian-French consensus is that radiotherapy should be used when progressive disease is documented in the absence of other alternatives, especially in sites where surgery can generate considerable morbidity, as in the head and neck.^{36,43} Adjuvant radiotherapy is specially suggested in patients with R1 or R2 resections, in whom the risk of local recurrence decreases, as well as in those with difficult-to-access tumors or who have refused surgical treatment, with the possibility of achieving local control in 70 to 93 % of cases.^{44,45}

Cryoablation

Cryoablation is used in extra-abdominal tumors, where up to 39 % complete response, 4 % progression and a low rate of complications is reported; however, it is not considered standard treatment, and more experience is still needed with this procedure.³⁸⁻⁴⁰

Isolated limb perfusion

This therapeutic modality is reserved for patients with progressive, unresectable disease or when surgery entails significant functional loss, especially in patients with distal or multifocal disease in whom systemic treatment has failed or who cannot receive it.⁴² Unlike other sarcomas, in patients with fibromatosis surgery is not recommended to control residual disease.⁴⁴

Prognosis

Table 2 presents the studies that have addressed the issue of prognosis and their main conclusions.

Quality of life

Different organizations, such as The Desmoid Tumor Research Foundation, as well as support groups

Table 2. Studies that report negative clinical factors for progression-free survival/recurrence-free survival in desmoid-type fibromatosis*

Study	Design	Participants (n)	Result	NPF (univariate analysis)	NPF (multivariate analysis)
Rock <i>et al.</i>	Retrospective	194 (187 received surgical treatment)	RFS	<ul style="list-style-type: none"> – Does not reveal statistical technique – Age (< 30 years) – Gender (female) – Location (calf, foot, supraclavicular fossa, gluteal muscle) – Surgical margin (R1/R2 vs. R0) 	
Huang <i>et al.</i>	Retrospective	151	RFS	<ul style="list-style-type: none"> – Gender (female) – Size (> 5 cm) – Location (abdominal wall > chest wall/back > extremities > head and neck) – Surgical margin (R1 vs. R0) – Recurrent – Number of tumors (single > multiple sites) 	<ul style="list-style-type: none"> – Size (> 5 cm) – Surgical margin (R1 vs. R0)
Salas <i>et al.</i>	Retrospective	426 (330 received surgical treatment)	PFS + RFS	<ul style="list-style-type: none"> – Age (< 37 years) – Size (> 7 cm) – Location (extra-abdominal, distal extremities) – Surgical margin (R2 vs. R1/R0) 	<ul style="list-style-type: none"> – Age (< 37 years) – Size (> 7 cm) – Location (extra-abdominal and distal extremities)
Merchant <i>et al.</i>	Retrospective	105	RFS		– None of the evaluated variables (age, gender, size, location, depth, use of radiotherapy)
Huang <i>et al.</i>	Retrospective	46	RFS		– Surgical margin (R1 vs. R0)
Crago <i>et al.</i>	Retrospective	495	RFS		<ul style="list-style-type: none"> – Age (< 26 years) – Size (> 10 cm) – Location (intra-abdominal/chest wall/extremities > abdominal wall) – Surgical margin < 5-cm tumors (R1 vs. R0)
Gronchi <i>et al.</i>	Retrospective	203	RFS		<ul style="list-style-type: none"> – Primary disease location (extremities) – Primary disease size (> 5 cm) – Recurrent disease
Spear <i>et al.</i>	Retrospective	107	RFS		<ul style="list-style-type: none"> – Age (< 18 years) – Positive surgical margin – Recurrent disease – Treatment only with surgery
Sorensen <i>et al.</i>	Retrospective	72 50 (extra-abdominal)	RFS	<ul style="list-style-type: none"> – Age (< 31 years) – Size (> 4 cm) – Adjuvant RT – Anatomic compartmentalization 	<ul style="list-style-type: none"> – Age (< 32 years) – Size (> 4 cm) – Extra-compartmental location – Surgical margin (R2/R1 vs. R0)
Fiore <i>et al.</i>	Retrospective	142 (83 on observation)	PFS		– None of the studied variables (age, gender, size, location)
Bertani <i>et al.</i>	Retrospective	62	RFS	<ul style="list-style-type: none"> – Size (≥ 10 cm) – Location (extremities) – Surgical margin (R1 vs. R0) 	– Location (extremities)
Colombo <i>et al.</i>	Retrospective	70	PFS	– None of the studied variables (gender, size, location)	

*Table obtained from Eastley N, McCulloch T, Esler C, Hennig I, Fairbairn J, Gronchi A, et al. Extra-abdominal desmoid fibromatosis: a review of management, current guidance and unanswered questions.⁴⁵

NPF: negative predictive factor; PFS: progression-free survival during non-surgical treatment; RFS: recurrence-free survival after surgical treatment.

in reference institutions, have created questionnaires to evaluate functioning and quality of life. Patients with desmoid tumors have decreased performance in all functional areas (physical, social cognitive and emotional), and are susceptible to periods of anxiety since diagnosis and during treatment.

Conclusion

Even when desmoid tumors are not able to generate distant disease and do not represent a direct threat to life, they can generate disability, chronic pain, functional deficit, psychological alterations and a significant decrease in quality of life. The unpredictable course, low incidence and unawareness of the disease have been limitations to advance faster in the knowledge of this pathology. The only way to do it is through information dissemination since the first contact with the patient, who should be individually and comprehensively addressed with multidisciplinary collaboration. Incorporation of molecular biology to clinical practice and the therapeutic process will allow increasing treatment personalization, in order to include each patient within a spectrum of manifestations of the disease and not as one more of such a heterogeneous group with such diverse results.

Conflict of interests

None

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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