Original Article

Surgery Section

Desmoid Tumours in Familial Adenomatous Polyposis: Review of 17 Patients from a Portuguese Tertiary Center

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ABSTRACT

Introduction: Desmoid Tumours (DT) are benign tumours with an estimated incidence of 2-4 per million per year. Between 7-16% of them are associated with Familial Adenomatous Polyposis (FAP) and are mostly parietal or intra-abdominal. They are a challenge in relation to their unpredictable natural course, associated complications and difficult treatment.

Aim: The aim of the present study was to review the occurrence, management and follow-up of DT on FAP patients treated consecutively at a tertiary care center.

Materials and Methods: A retrospective review of clinical data from patients treated consecutively between 1993 and 2014. Patients' data was gathered from clinical records. Data collection included the following variables: demographic data, genotype, FAP phenotype, data on FAP related surgery, DT diagnosis, location, size and number, DT treatment, patients' status and follow-up data.

Results: The study population consisted of 17 patients from 9 families; with a mean age of 41 years, mostly women (59%) and most with a mutation either on codon 232 or 554. Most tumours had an intra-abdominal component (59%) with a mean size of 5cm. Fifteen patients were first treated with pharmacotherapy (Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Tamoxifen). Five patients (29%) underwent surgery, 4 of them for complications of intra-abdominal tumours and 1 patient for abdominal wall tumours. Two patients underwent chemotherapy in relation to aggressive intra-abdominal disease. The mean follow-up time since diagnosis of DT was 123 months. Overall, 2 patients had remission, 11 patients had regression or stabilized disease, and 2 patients had progression. One patient died due to surgical complications.

Conclusion: Diagnosis of DT is based on clinical symptoms, without the need for screening, although imaging plays an important role once diagnosis is suspected. The treatment approach is conservative on most patients, leaving surgery for DT related complications. The follow-up of patients with DT is also based on clinical symptoms.

Keywords: Aggressive fibromatosis, Fibroproliferative diseases, Infiltrative nature

INTRODUCTION

Desmoid Tumours (DT), also known as aggressive fibromatosis, is part of a group of fibroproliferative diseases. They result from the proliferation of monoclonal cells of fibroblastic origin. They don't metastasize, hence they are not considered malignant. They can however be aggressive due to their infiltrative nature, possible multifocality and tendency to recur [1-5].

These tumours are rare, with an estimated incidence of 2-4 per million per year [4]. They are mostly sporadic but between 7-16% are associated with Familial Adenomatous Polyposis (FAP), as part of Gardner's syndrome [1,6,7]. DT are an important cause of morbidity and mortality in patients with FAP, occurring in 12-15% of these patients [1,8].

FAP is related to mutations on Adenomatous Polyposis Coli gene (APC), which is a tumour suppressor gene. APC protein degrades β-catenin, which is implicated in cell proliferation regulation. The truncated APC protein is unable to perform its function appropriately [9]. The mutation site on the APC gene is associated to FAP phenotype, including DT development. The more distal the mutation (closer to 3' end), the higher the risk of the patient being affected by DT [1,9,10].

Other factors involved in the development of DT are previous abdominal surgery and family history of DT [11,12]. Female sex has been reported as a risk factor but findings are not consistent [11,12].

Despite the possibility of DT arising in any location, DT related to FAP are mostly on the abdominal region: intra-abdominal, on the abdominal wall and "transabdominal" [1,7].

Some of them take a benign course, with indolent evolution, stabilization of growth or even remission. Others show an aggressive behaviour with rapid growth and mass effect on surrounding structures, particularly in case of intra-abdominal DT. Possible complications of intra-abdominal DT are intestinal obstruction, ischemia, haemorrhage and perforation or ureteric obstruction [1,4,8].

When DT develops in FAP patients, they are the second most common cause of mortality [13]. DT are challenging because of their unpredictable natural course, associated complications and difficult treatment. The aim of the present study was to review the occurrence, management and follow-up of DT on FAP patients treated consecutively at a tertiary center.

MATERIALS AND METHODS

This was a retrospective review of a cohort of patients with FAP, treated consecutively at a Digestive Surgery Unit of a single tertiary referral center, between 1993 and 2014, who developed DT. Patients underwent clinical evaluation every 6 months.

The study was approved by the general surgery scientific commission and institutional review board. We consulted patients' clinical records and gathered data with full anonymity.

Data collection included the following variables: demographic data (age, sex), genotype (APC mutation), FAP phenotype, data on FAP related surgery (age, type of surgery), DT diagnosis, location, size and number, DT treatment, patient's status and follow-up data. Considering the location of tumours, if a patient had at least one tumour with an intra-abdominal component, we classified them as *intra-abdominal*.

Patients were also staged according to Church et al., which is a proposed staging system for intra-abdominal DT [8]. This staging system allows stratification of this set of patients by disease severity. In case of multiple DT, the clinically more relevant lesion was used to classify the disease.

RESULTS

Our population consisted of 17 patients, belonging to 9 families, most being women (59%) with mean age of 41years. Ten patients belonging to 2 families had mutations on codon 232 and 554 (5 patients each). Five patients from different families had mutations on codons 554, 625, 1009, 1309 and 1465. The APC mutation could not be determined on 2 unrelated patients. These patients were also tested for MUTYH gene mutations and microsatellite instability with negative results. Patients with mutation on codon 232 (all from same family) had attenuated FAP. All other patients had classic FAP.

[Table/Fig-1] gives an overview of our population of FAP patients with desmoids. All patients underwent prophylactic colorectal surgery before diagnosis of DT. The FAP related surgery was a coloprotectomy with ileoanal pouch in 10 patients (59%) or a colectomy with ileorrectal anastomosis (41%) according to rectal presentation of the disease. The mean time between surgery and the first DT diagnosis was 60months (6-94months), with a mean age of 30 years at DT diagnosis.

The diagnosis was first suspected clinically in 13 patients (76%) on palpation of an abdominal mass and then confirmed and characterized by Computed Tomography (CT) scan. Three patients presented with ileoanal pouch dysfunction and were investigated with CT scan. One patient had diagnosis during surgery for Gastrointestinal Haemorrhage (GIH).

Ten patients (59%) had intra-abdominal tumours with a mean size of 5cm, while the rest were located on the abdominal wall (41%) with a mean size of 4.5cm. One patient developed 1 intra-thoracic tumour diagnosed during follow-up. [Table/Fig-2] presents more information regarding intra-abdominal tumours.

Fifteen patients were first treated with pharmacotherapy [Table/Fig-1,3]. Pharmacotherapy consisted of Non-steroidal Anti-inflammatory Drugs (NSAIDs) as first line of treatment– sulindac until it was discontinued in Portugal in 2008, and then celecoxib. Tamoxifen was the second line of treatment, mostly associated with NSAIDs, usually with progressive dosing as required, up to 120mg/day. Two patients didn't tolerate NSAIDs; one because of profuse diarrhea, the other had ileoanal pouch bleeding. The former stayed on tamoxifen alone, the latter had no therapy since he remained asymptomatic and the tumour remained stable. Ten patients (59%) underwent pharmacotherapy as the sole treatment during follow-up time. The remaining patients underwent either surgery or chemotherapy, except one patient who had a recent clinically detected abdominal wall DT. He had a pericentimetric tumour and was asymptomatic. He was left untreated at the time of diagnosis, in order to assess the presence of other DT at different locations by CT scan.

Five patients (29%) have been submitted to DT related surgery. Despite different initial staging [Table/Fig-3], the indication for surgery was related to complications on 4 patients which had intra-abdominal DT – they all evolved to stage IV disease:

- One patient was initial stage III - slow growing of DT – and started NSAIDs at diagnosis. On the second year of DT follow-up, the patient had a small bowel perforation associated with bowel erosion by the tumour. An enterectomy was performed and the resection was considered R2. The patient died of septic complications in the late post-operative period, without anastomotic leakage.
- One patient started NSAIDs and tamoxifen once diagnosed with intra-abdominal DT. Nine months later, the patient progressed from stage I to stage IV and underwent emergent surgery for GIH– R0 resection.
- One patient was diagnosed at the time of emergent surgery. The patient underwent a R2 resection and needed chemotherapy.
- The fourth patient who underwent surgery for intra-abdominal DT

N*	Sex	FAP Surgery	Age (years)		DT Location	DT treatment	Months of follow-up	Outcome
			FAP surgery	DT diagnosis				
1	F	IRA†	37	38	AW§	NSAID's / surgery	216	Progression
2	F	CPIP‡	25	26	IA‖	NSAID's	216	Remission
3	F	IRA	27	28	IA	NSAID's / tamoxifen	216	Stable
4	M	CPIP	25	28	IA	NSAID's / tamoxifen	204	Stable
5	F	CPIP	39	43	IA	tamoxifen / surgery	141	Stable
6	M	IRA	32	36	AW / IA	surgery / chemo**/ NSAID's	146	Stable
7	F	IRA	29	29	AW	NSAID's	144	Stable
8	F	IRA	54	54	IA	NSAID's/ surgery	36	Death
9	F	CPIP	18	19	AW	NSAID's / tamoxifen	108	Regression
10	F	CPIP	20	31	IA	NSAID'S / tamoxifen / surgery	106	Remission
11	M	CPIP	17	18	AW	NSAID's / tamoxifen	106	Progression
12	M	IRA	18	19	AW	NSAID's	67	Stable
13	F	CPIP	17	30	IA	NSAID's	72	Stable
14	M	IRA	33	47	IA	NSAID's	252	Regression
15	F	CPIP	22	22	AW / IA	NSAID's/ tamoxifen / chemo	30	Regression
16	M	CPIP	18	19	AW	NSAID's	29	Stable
17	M	CPIP	19	22	AW	-	6	Stable
Total	**N**	**N**	**Mean**	**Mean**	**N**	**N**	**Mean**	**N**
17	10 F 7 M	10 CPIP 7 IRA	26	30 (19-54)	8 - IA 7 - AW 2 - AW / IA	15 - NSAID's 7 - tamoxifen 5 – surgery 2 - chemo	123 (6-252)	9 - stable 3 - regression 2 - remission 2 - progression 1 - death

[Table/Fig-1]: Population overview: demographic, clinical, treatment and outcome data of FAP patients With DT.
*N- refers to number of patients †IRA – colectomy with ileorrectal anastomosis ‡CPIP – coloprotectomy with ileoanal pouch
§AW – abdominal wall ‖IA – intra-abdominal **chemo – chemotherapy

Number of DT	Number of patients
1	5
2	4
>2	1
Staging (Church	
I	4
II	-
III	4
IV	2
Time between surgery and diagnosis	**Months:** mean (min-max)
All patients	60 (2-372)
stage I	279
stage II	-
stage III	24
stage IV	69

[Table/Fig-2]: Characterization of intra-abdominal DT at diagnosis.

Staging *	Treatment$	Number of patients
I	NSAIDs	2
	Tamoxifen - surgery	1
	NSAIDs and tamoxifen –surgery	1
II	-	0
III	NSAIDs	1
	NSAIDs and tamoxifen	2
	NSAIDs –surgery	1
IV	NSAIDs and tamoxifen - chemotherapy	1
	surgery – chemotherapy – NSAIDs	1

[Table/Fig-3]: Management of patients.
* initial staging $ at any point

was also stage I at the time of diagnosis. He was given NSAIDs but they were not tolerated (profuse diarrhea). For 7 years this patient's therapy consisted of tamoxifen with regression of DT. She then progressed to stage IV, presenting extensive portal venous gas in relation to small bowel and mesenteric venous erosion by DT – a complete resection was performed.

- Only one patient with abdominal wall DT had surgery [Table/Fig-1], based on referred discomfort, having two DT resected with histologic free margins. Both DT recurred on this patient, who also developed an intra-abdominal and intra-thoracic DT. The patient is currently treated with NSAIDs and tamoxifen.

Both patients with histologically free margins had DT recurrence and started pharmacotherapy. One patient is in remission while the other remains stable.

Only 2 patients underwent chemotherapy in relation to aggressive intra-abdominal disease, with progressive symptoms, and no response to NSAIDs or tamoxifen. Both patients were stage IV at presentation. One patient was already described and underwent surgery as first treatment but the other patient had no indication to surgery based on aggressive disease with no chance of resection free of iatrogenic complications. Chemotherapy regimen consisted of doxorubicin and dacarbazine, on both patients. Both had regression of disease and they are asymptomatic.

The mean follow-up time since diagnosis of DT was 123 months. Information about current patient status is presented on [Table/Fig-4].

Patient status	Number of patients
Dead	1
Symptomatic	1
Asymptomatic	15

[Table/Fig-4]: Patients status.

DISCUSSION

Our population of 17 patients from a single institution is in line with DT prevalence on FAP patients. The largest series reported are from multi-institutional or national studies [11]. Nieuwenhuis et al., reported 78 patients from a national Dutch Polyposis Registry [14].

The most important risk factors for the development of DT are previous surgery, family history and the position of the mutation on the APC gene [1,9-12,16]. There is no current evidence associating the type of surgery and the occurrence of DT. All patients from our population have been submitted to prophylactic colectomy/coloprotectomy before the diagnosis of DT.

Ten of our patients (59%) belong to 2 families which is consistent with what is called family clustering [11,15,16]. Studies showed that tumours tended to cluster in susceptible individuals with a strong family history of DT, irrespective of the germline APC mutation [15].

It is known that the phenotype of FAP is related to the position of the APC gene mutation [9]. Regarding extra colonic manifestations of FAP, some patients are affected more severely than others, depending on the site of the mutation [10]. There is some evidence that mutations on the 3' end of the APC gene, particularly distal to codon 1399, might be associated with a greater tendency to development of DT, but findings are not always consistent [9,10,15]. This study population had a high frequency of proximal mutations (closer to 5' end) on the APC gene. Only 2 patients had mutations within the hotspot region between codons 1250 and 1464 [9]. This mutational pattern is not frequently reported on FAP patients with DT development [9].

According to Church et al., patients which have the shortest interval between surgery and DT appearance have the highest staging [8,17,18]. There seems to be such a relation on this study population. Patients classified as stage I have clearly the longest interval from surgery to DT diagnosis [Table/Fig-2].

The diagnosis of FAP related DT is made clinically in relation to a mass on the abdominal region, while investigating symptoms or incidentally on imaging or surgery. In this study population most DT were detected clinically, but four patients with intra-abdominal tumours were diagnosed by CT scan, during the investigation of ileoanal pouch dysfunction. Such presentation should prompt investigation and imaging is essential because DT is a possible aetiology, particularly in known affected families. CT is the most common image modality for diagnosis confirmation, identifying other DT and their characterization, such as determining the extent of invasion onto vital structures [4]. All of our patients underwent CT for this purpose. MRI might be useful when elective surgery is contemplated for an intra-abdominal DT [4]. There is no recommendation to actively search for DT on FAP patients, since they are benign and their clinical importance is related to symptoms. Although rare, it is possible for a DT to present itself as a life threatening complication, such as a GIH as reported in this study.

Treatment for DT may be challenging. Surgery has been advocated as the gold standard whenever feasible [1,3,19]. Currently, many authors consider medical treatment or even a wait-and-see approach on the management of these patients, since >50% have a slow growing or potentially regressive disease [5]. In fact, the Italian and French Sarcoma Group review, contemplate a wait-and-see approach for most patients [5].

There are some questions when considering a low threshold surgical approach. First of all, DT shows a variable behaviour and so far there are no reliable factors that predict it. Surgery itself is a possible trigger of further tumorigenesis [11]. Even though free histologic margins seem to be a prognostic factor of local recurrence, there are reports that show a less clear relation [4,5,20-

22]. Recurrences might occur after complete resections. Moreover, patients that develop recurrence after surgery may remain stable without further treatment [3]. As such, negative margins should be achieved only if not associated with increased morbidity.

In this study there is only one abdominal wall DT resection reported. The margins were negative but the patient had recurrence. At that time the decision to perform surgery was based on the available literature. The evidence that most patients did not have progressive disease, led us to a conservative non-surgical approach for the remainder of patients with abdominal wall DT.

However, FAP related DT is mostly intra-abdominal [13]. The usual infiltrative pattern of mesenteric DT poses difficulties regarding surgery. The required complex surgeries, most often with incomplete resections, the high risk of iatrogenic injuries, the possibility of intestinal failure and the uncertainty of results, are major drawbacks to perform surgery on such patients [15,22-24]. Surgery should be planned if complications are eminently expected or actually happen.

We performed surgery only on four patients with intra-abdominal DT, all because of complications, most notably gastrointestinal haemorrhage and perforation.

There are various options for medical treatment of DT despite a lack of full knowledge of their mechanisms of action [25]. Currently there are no randomized trials comparing different options.

The most common medical treatment consists of NSAIDs. Indomethacin and sulindac (long-acting analogue of indomethacin), have been tested with variable reported responses [4,26]. Celecoxib, frequently prescribed for control of duodenal and colic adenomas, is also used for DT treatment but there is no clear evidence of its role on this setting [27].

There is some evidence that oestrogen stimulate growth of DT. As such, hormone therapy has been investigated and described as effective in the treatment of DT, particularly Tamoxifen [4,20,26]. Tested doses are as high as 120mg [26].

The combination of hormone therapy with NSAIDs is widely used since it is associated with low toxicity and possibly better outcome than isolated therapies [4]. We have used NSAIDs on most patients and used them associated with tamoxifen on patients who did not respond or did not tolerate NSAIDs. We did not use this strategy on 2 patients. One patient underwent emergent surgery for stage IV disease while the other patient had the clinical diagnosis of a small parietal asymptomatic DT three months ago and still awaits better characterization with a CT scan to evaluate the adequate therapy, including a possible wait and see approach.

Radiotherapy (RT) is considered a useful adjuvant therapy for DT, particularly when there are positive or close surgical margins. There are limitations to the use of RT in FAP patients, because most DT are located in the abdomen, and on this location, it is associated with serious side effects. We did not offer this treatment to any patient.

Imatinib has been studied, as well as other tyrosine kinase inhibitors. So far results vary between stabilization and 15% response rates. Its use is only justifiable in a trial setting [4,25].

Interferon has been scarcely reported as an optionand currently is not recommended [4,26].

Cytotoxic chemotherapy is reserved for patients with aggressive disease, who don't respond to less toxic treatment and when DT are not amenable to resection. The major concern is its use for a benign disease on a generally young population, and its late side effects. The French Sarcoma Group has reviewed the effect of chemotherapy in patients with DT and concluded there is a clear benefit, particularly with anthracyclines, despite side effects [28]. Our regimen consisted, on both patients, of doxorubicin and dacarbazine which is a common protocol on this setting [28]. Other common protocol is methotrexate and vinblastine/vinorelbine, considered safer in terms of toxicity profile [5,28]. There are no follow-up recommendations on these patients in the literature.

CONCLUSION

Diagnosis of DT in PAF patients is based on clinical symptoms, without the need for screening, although imaging plays an important role once diagnosis is suspected. The treatment approach is conservative on most patients, mainly with NSAIDs and tamoxifen, leaving surgery for DT related complications. Most patients follow an indolent path. The follow-up of patients with DT is also based on clinical symptoms.

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