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Desmoid Tumours in Familial Adenomatous Polyposis

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The term desmoid was first used by Muller [1] to describe the tendon-like aspect and the hard consistence of this type of proliferation (desmos in Greek means band). Desmoid tumours (DTs) are classified as extra- or intra-abdominal. The extra-abdominal DTs arise from fascial or muscoloaponeurotic structures predominantly of the abdominal wall (Fig 1a, 1b, 1c) and occasionally of the shoulder girdle, chest wall, inguinal region and extremities.

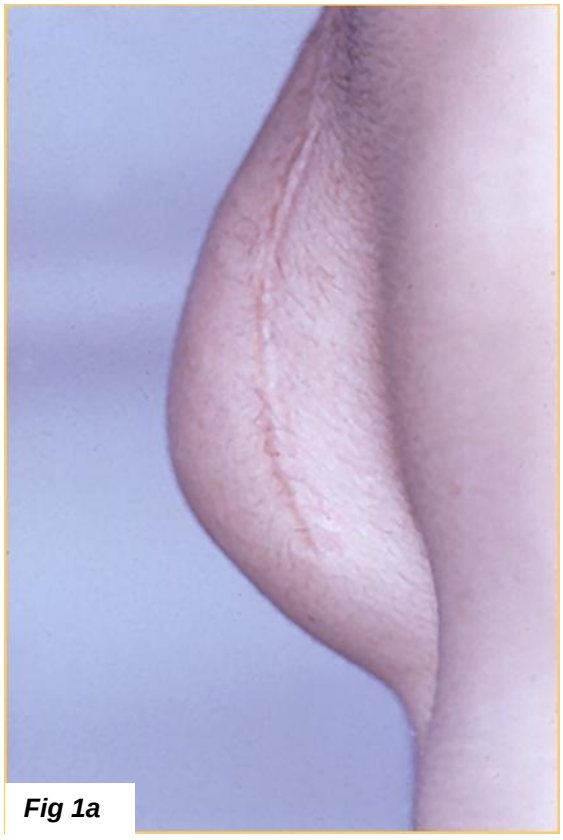

Fig 1a

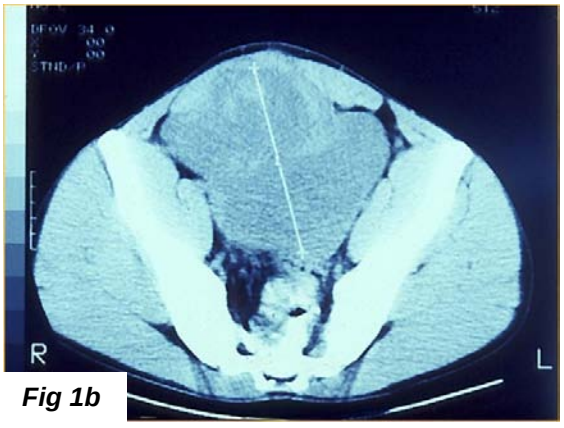

Fig 1b

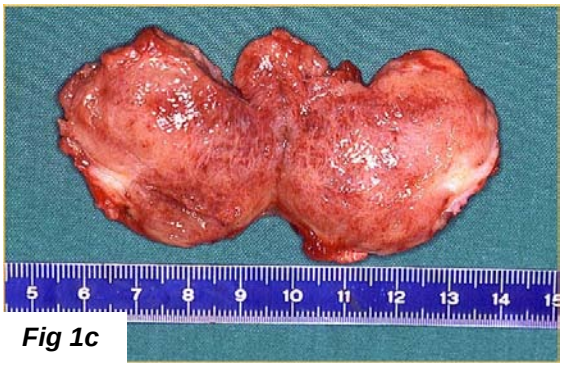

Fig 1c

The intra-abdominal DTs develop in the folds of the mesentery or the mesocolon (Fig 2a, 2b) even reaching the retroperitoneal tissue or they may grow exclusively in this region.

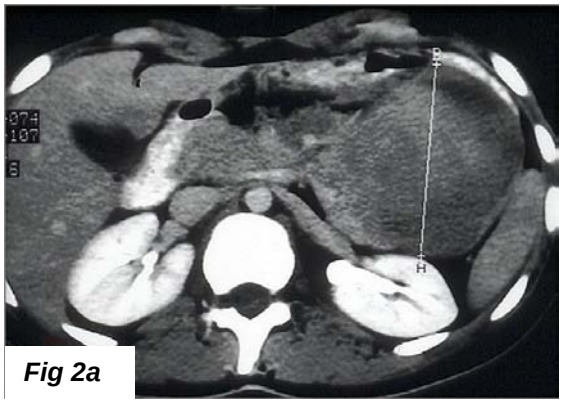

Fig 2a

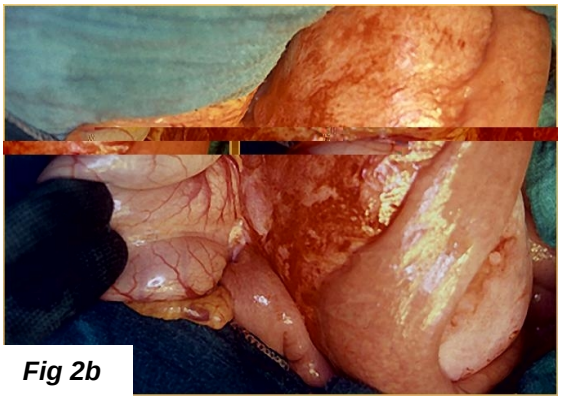

Fig 2b

These proliferations are usually single, round or oval in shape, up to 60 cm in size. Rather than a mass, a thickening of the mesentery that appears to be covered with hard, white spots and causes retraction of the peritoneal folds is frequently reported in familial adenomatous polyps (FAP) patients. This process has been variously referred as mesenteric fibrosis or mesenteric fibromatosis [2-4]. However, whitish, thin plaque-like areas of the mesenteric folds have been frequently identified in FAP patients undergoing laparotomy (Fig 3).

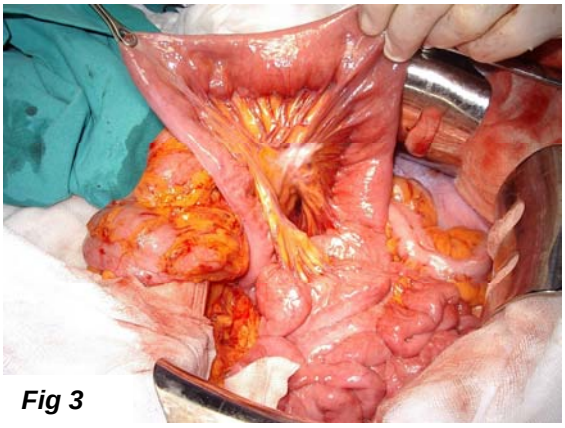

Fig 3

It has been suggested that these mesenteric abnormalities represent precursor lesions of mesenteric fibromatosis and mesenteric DT [5,6]. A model of stepwise progression for DT development similar to the adenoma-carcinoma sequence observed for colorectal cancer has been proposed. A prospective study of 42 patients with FAP undergoing laparotomy was made performing a detailed examination of the small bowel mesentery and biopsy of the lesions. Plaque-like areas of peritoneal thickening were observed in 30% of these patients and areas of diffuse mesenteric fibromatosis in 16%.

The patients with mesenteric fibromatosis had undergone a significantly higher number of previous abdominal operations than those without [5].

Helical abdominopelvic CT scanning and MRI was employed to characterise and follow up these precursors. It has been suggested that rapidly growing DTs have high signal intensity on T2-weighted images [7]. Mesenteric fibromatosis were identified in 21% of asymptomatic patients.

At the follow-up (median 27 months) patients with desmoid precursor lesions (DPLs) had a significantly greater degree of mesenteric fibromatosis and DT formation than the control group [6]. Furthermore, CT findings consistent with mesenteric fibromatosis were observed on reviewing the scans of patients subsequently developing DTs [8].

While DTs are rare in general population (2-4 cases/million/year), they represent a major extra-intestinal manifestation of FAP.

The risk for a FAP patient of developing a DT is one thousand times that of the general population [2].

The incidence increases steadily with age until the fifth decade of life [9]. Only a few patients manifest a DT before the diagnosis of colonic polyposis.

The growth of DTs usually occurs after the colectomy and the mean age at diagnosis varies between 29 and 32 years in patients collected in the registries of the most important Institutions [2].

The cumulative risk of DT developing 10 years after prophylactic colectomy is 16 % and the cumulative life-time risk is around 21% [10].

The true incidence of DTs in FAP is unknown. The incidence usually ranges between 7 and 12% when a retrospective review of surgical FAP series is considered [2,10, 11].

In these studies the diagnosis is generally made on clinical evidence of an abdominal mass.

However, considering that several mesenteric DTs are asymptomatic or are discovered fortuitously on radiographic abdominal examination, the incidence is probably higher than usually reported. Furthermore, it is not clear whether mesenteric fibromatoses are always considered in these clinical series.

Clinical Presentation

Desmoids can remain asymptomatic for a considerable length of time, all the while relentlessly enlarging and infiltrating adjacent structures. However, DTs may show a capricious, variable clinical behaviour, usually characterised by an indolent course, rarely by a spontaneous regression and sometimes by an aggressive and rapid growth and a tendency to invade surrounding structures. DTs may cause abdominal pain, nausea, vomiting, diarrhoea and deterioration of the functional result in patients submitted to restorative surgery after total colectomy.

The intra-abdominal tumour growth may induce small bowel obstruction or other life-threatening complications such as intestinal perforation or intestinal infarct as the result of the compression of the blood vessels which may impair vascular supply and cause small bowel ischaemia or mesenteric thrombosis [12, 13]. The consequences of mucosal ischaemia of the small bowel are bleeding or intestinal strictures [14]. Sudden enlargement of the DT can provoke deep vein thrombosis and fatal pulmonary embolism [15].

The tumoral mass may undergo colliquative necrosis and abscess formation which can determine an abdominal emergency or a spontaneous discharge into the intestinal lumen with fistula formation.

Also mono- or bilateral hydronephrosis as a result of retroperitoneal invasion can be observed.

DT is the second most common cause of death in FAP patients after colorectal cancer [16-18]. Intra-abdominal DTs can be responsible of death in up to 11% of FAP patients [16-18].

In the experience of the Johns Hopkins University, the survival rate from DT evaluated by lifetable analysis is 93% at 5 years and 79% at 20 years with a mean age of death in the affected patients of 40 years [2].

Patients who have had an ileal pouch-anal anastomosis (IPAA) and have developed a DT show a worse functional result than IPAA patients not developing a DT [19-20].

The occurrence of small bowel obstruction or intestinal bleeding in IPAA patients with DTs usually require the removal of the pouch [14, 19].

Aetiology and Risk Factors

The aetiology of DTs is unknown and their true nature is controversial. DTs are considered dysplastic lesions of connective tissue and classified as fibromatoses which cover diseases such as Dupuytren's contracture, Peyronie's disease, plantar fibromatosis, idiopathic retroperitoneal fibrosis, etc. The absence of metastatic spread, the generally benign behaviour with slow growth or even regression, the histological features consisting of mature fibroblast without atypia or mitoses, and the absence of telomerase are consistent with a reactive or dysplastic lesion. However, their potentially rapid and aggressive growth and their tendency to recur after surgical removal have suggested a neoplastic origin. Favouring this view is also the fact that DTs will arise after inactivation of the *APC* tumour suppressor gene, occurring by point mutation or allelic deletion. Furthermore, it has been observed that the majority of the cells are represented by a clonal population [21]. It has also been shown that the proliferation of desmoid cell cultures is inhibited by the cellular transfection of wild-type *APC* [22]. The hypothesis has been proposed that the DPLs undergo a multi-step process analogous to the cascade suggested for the adenoma-carcinoma sequence developing firstly mesenteric fibromatosis and finally mesenteric

DT [5, 213]. The surgical trauma could favour somatic mutations of mesenteric fibroblasts, inducing their clonal expansion to produce a DT. This interpretation suggests the need of preventive measures in order to avoid the transformation of DPLs in true DTs, as well as for a rational oncological approach to aggressive DTs.

Gender and Pregnancy

A clear preponderance of DTs among females clearly has been noted in studies concerning large series of FAP patients and females have twice the odds of developing DTs compared with males [10, 26].

The effect of pregnancy on the behaviour of intra-abdominal DTs has been investigated in retrospective studies. Some Authors have shown a tendency for DTs to develop soon after pregnancy [23,27,28], but others find that DTs present later, are smaller and significantly less aggressive in females who have been pregnant than in females who have not [29]. These Authors suggest that hormones of pregnancy, such as progesterone or prolactin, could have a beneficial effect and suggest that this type of hormonal treatment should be attempted.

In their opinion further prospective studies are needed to determine the consequences of pregnancy on DTs and the risk for a pregnant female of developing a DT, in order to advise women with a family history of DT against pregnancy [29].

Surgery

A surgical trauma is generally indicated as a precipitating factor for DT development (Table 1). In particular, in 68-83% of FAP patients an abdominal operation precedes formation of DT by some months up to a few years. The mean time to DT development varies, but it is usually around 2 years [3,9,23,30].

It appears that there is not correlation between the entity of the surgery and the occurrence of DT. DTs affect patients operated by subtotal colectomy and ileo-rectal anastomosis or by restorative proctocolectomy and IPAA in similar percentage [11,24,25,31], but even a minor abdominal surgical procedure such as appendectomy can induce DTs.

Iterative surgery can increase the risk as Penna et al. [11] have shown, considering that 41% of DTs are discovered after at least two surgical interventions.

Early age at time of colectomy represents a risk factor.

In the experience of Jarvinen [9], patients with postoperative DTs had undergo colectomy at a mean age of 26.1 years, significantly earlier than those not developing DTs (37.8 years, $p<0.01$).

Family History and Genetic Predisposition

The hereditary nature of DT has become clearer when DT and mesenteric fibromatosis were recognized as stigmata of the FAP and a more accurate diagnosis of these complications was achieved. DTs have been reported to be frequently associated with Gardner's syndrome [4]: a 32% incidence of desmoid reaction is found among affected members of the original Gardner's syndrome kindred 109. First degree relatives of FAP patients with DTs have a greater risk of developing DTs than more distant relatives (

25% for first degree vs. 11% for second degree and 8% for third degree) [32].

Bertario et al [18] estimated the risk of developing DTs in 897 FAP patients scheduled on the Italian hereditary colorectal tumour registry and found that family history of DT, osteomas and epidermoid cysts was significantly associated with the presence of the disease. Similarly, Sturt et al [26] found that family history (especially if more than 50% of the members were affected with DT) increased the odds ratio over sevenfold.

The *APC* gene responsible for the development of FAP has been investigated for specific mutations which may be related to DT development. DTs will develop when both alleles of the *APC* gene are faulty, but one of the mutations encompasses the region 3' of codon 1444 [26,33,34]. Genotype-phenotype correlation within the location of *APC* mutation, the occurrence of DTs and the number of colonic polyps has been observed: *APC* mutations between codons 1444 to 1578 is associated with DTs and a severe form of polyposis, while mutations at the 3' region of *APC* are linked with DTs and an attenuated form of FAP [35,36]. An aggressive growth pattern of DTs has been attributed to the presence of a germline *APC* mutation in codon 1445-1578 [35].

Mutations beyond codon 1309 or 1444 confer, respectively, a 17- and a 12-fold higher risk of DT development, compared with mutations located at or before codon 452 [10]. Therefore, families with a high incidence of DTs usually have the inherited germline mutation at 3' of codon 1444 and may have the environmentally induced somatic mutation in any point of *APC* gene, whereas families with sporadic occurrence of DT have the germline mutation at 5' of codon 1444 and must have the somatic mutation at 3' of codon 1444. This fact explains the difference in the percentage of DTs among *APC* kindreds.

An uncommon mutation of the *APC* gene due to frameshift of codon 1924 is accompanied by a high incidence of DTs, a few or no colonic polyps and the rare occurrence of colorectal cancer. This syndrome is called Hereditary Desmoid Disease [37].

Desmoid and Oestrogen

The oestrogenic bio-effects are mediated by specific receptor subtypes, ERα and ERβ, that exhibit a tissue-specific distribution.

The unbound ERs exist as inactive intracellular receptors expressed in reproductive and not reproductive tissues.

The mechanism of action is switched on after the interaction of the receptors with the ligand(s), that could be either the steroidal oestrogen, the polyphenolic phyto-oestrogens or the synthetic SERMs (Selective Estrogen Receptor Modulators).

The latter exhibit both agonist or antagonist oestrogenic actions.

The first generation of SERMs are represented by the triphenylethylenes tamoxifen and toremifene, which show agonist properties in the bone and uterus, but an antagonist action on the breast.

The last generation of SERMs, represented by raloxifene and its analogues (LY-353381, EM-800 and CP-336156), are benzothiophene derivatives, showing anti-oestrogenic effects on the breast and uterus, but an oestrogen agonist effect on bone and cardiovascular systems.

Treatment with Serms

Anti-oestrogen therapy has been largely based on triphenylethylenes such as tamoxifen or its chlorinated derivate toremifene since the first use by Waddell in 1983[38]. As for the use of NSAIDs, medical treatment with SERMs is empirical and controversial, being based largely on anecdotal reports and small, poorly controlled studies, most of which are retrospective [39]. The dose commonly used is 30 mg/day which is accompanied by a positive effect in about 50% of the cases. Other Authors have employed higher doses of tamoxifene (120-200 mg/day) obtaining a cessation of growth in 63-77% of the patients [40,41]. However, the best outcome was observed in the group of patients who received high-dose tamoxifen in combination with sulindac 300 mg. Development of ovarian cysts is a frequent side-effect of tamoxifen treatment in the female patients. The response to tamoxifen is usually gradual and slow so that the achievement of a partial or complete regression lasts several months or years. If DTs are particularly aggressive with rapid growth, the effect of SERMs could be negative in the first months because the time period required for the action can be prolonged. It is not clear how long the treatment should be once a complete regression has been obtained. The likelihood of accelerated DT growth on the cessation of tamoxifen treatment should justify a prolonged or indefinite treatment [40]. However, the risk of endometrial cancer with 20 mg per day of tamoxifen has been recognized for many years [42,43]. Conversely, lack of the worrying endometrial stimulation seen with triphenylethylenes confers to raloxifene a more favourable profile, particularly in the long-term use of the drug. We studied the effect of 120 mg daily (a dosage double than recommended for prevention of osteoporotic fractures) of raloxifene on progression of DT and of mesenteric fibromatosis by evaluation of lesion size and symptoms in 13 FAP patients. The patients had a significant response to raloxifene therapy with complete remission in 5 cases and partial remission in 5 other cases [44]. None of the patients experienced major side-effects and no significant changes in biochemical parameters or endometrial thickness were observed.

It is important to bear in mind that raloxifene was efficacious even if previous treatments with tamoxifen and sulindac had failed. Table 2,3 focuses our personal experience respectively on chemoprophylaxis and on drug therapy.

NSAIDS and Desmoid Tumors

The fact that both ß-catenin and mutated *APC* are implicated in colon cancer and DT development [45,46] and that prostaglandins and cyclooxygenase have a role in colonic neoplasia and FAP progression [47-50] has prompt the use of NSAIDs in the treatment of DTs. However, there are enough differences between desmoids and colonic neoplasms so that data, including blockade of angiogenesis, modulation of aromatase, and pro-apoptotic activity,. cannot be easily generalised from one tumour to another. We showed that there was a high expression of COX-1 and COX-2 in DT cells and tissues derived from different patients undergoing surgery (Picariello et al., personal communication, 2006). In particular, the amount of COX-2 protein was higher than that of COX-1, suggesting the role of COX-2 in the pathogenesis of this neoplasia. In addition, the expression of COXs was different in the different cultures, suggesting an extreme variability between individual tumours. Indomethacin or sulindac, an indomethacin analogue with prolonged effect, has been frequently used alone or in combination with anti-oestrogens. The mechanisms of action of

the anti-COX drugs are complex: sulindac sulphide, the pharmacologically active metabolite of sulindac, induces a significant growth reduction in desmoid cells in vitro [51] , but the drug does not induce apoptosis at clinically significant concentrations in these cells. However, this NSAID molecule induces apoptosis in an endothelial cell line. The latter effect seems very important considering the role of the microvasculature in tumour growth and could explain the efficacy of sulindac sulphide in the treatment of DTs. Other recent studies have also shown that in DT cell cultures the inhibition of COX-2 expression with a new coxib, DFU (5,5-dimethiyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(5H)-furon one), blocks the cellular growth, but does not promote apoptosis, suggesting that regulation of apoptosis does not play a major role in this neoplasm [93] and calling for other mechanisms to explain the effect of this drug.

Several small series of patients have been treated with a daily dosage of 200-400 mg of sulindac. The duration of treatment varied from a few months to several years. Overall, an objective response rate of about 50% was observed: in the majority of the patients a partial regression was shown and only in few patients a complete regression was obtained [52,53,54]. This treatment seems less efficacious in patients undergoing partial resection of their DT prior to medical therapy [31]. Most responses were observed after few weeks of treatment.

More often sulindac has been employed in combination with anti-oestrogen even if the effect is similar to that observed in patients treated with sulindac alone. Recently, 11 patients were treated with a combination of celecoxib, an anti-COX2, and tamoxifene, showing a complete regression in 1 patient, a partial regression in 3, a stable disease in 5 and no tumour recurrence in 2 patients in whom the drugs were used as adjuvant therapy after surgical excision [15] . As anticancer therapy, coxibs present important theoretical advantages: they are orally active, have moderate side-effects, and have few medical contraindications. Their good toxicological profile allows long-term medical treatment. In conclusion, even if the small number of cases studied and appropriately referred in the literature and the absence of prospective randomised trials make estimation of the effect of NSAIDs difficult, they can be effective in controlling the DT growth and should be used as a first-line treatment.

Other Drugs

A very small number or anecdotic cases are treated with other drugs sometimes in combination with NSAIDs or SERMs: warfarin and vitamin K [96], interferon-α-2b , progesterone, prednisolone , ascorbic acid, testosterone, analogues of LHRH, and pirfenidone [55-58]. Recently, imatinib mesylate has been shown to be active in two no-FAP patients with extra-abdominal DT refractory to other medical treatments. Interestingly, positivity for c-kit as well as PDGFR-α and PGDFR-β was found at immunohistochemical and qualitative RT-PCR analysis [59] These data must be confirmed on DTs in association with FAP and on a larger series.

Prevention of Desmoid Tumours

Chemoprohylaxis against the onset of DTs has been suggested even if no data are reported in the literature. The ideal drug should be active in a large number of cases and have a favourable therapeutic index. Both NSAIDs and SERMs seem to have these

characteristics, and raloxifen has no major side-effects. All the FAP patients submitted to abdominal surgery who have a family history for DT or a 3' *APC* mutation are candidates for a pharmacological prophylaxis. In our opinion, the patients in whom PDLs are found at surgery should also be submitted to chemoprophylaxis.

Our experience is detailed in Table 2.

The 20 patients with a DPL or a fibromatosis of the mesenteric fold were treated with tamoxifen or raloxifen and followed up for a mean time of 65 months and 79 months, respectively.

No progression of the desmoid disease was observed in any patient and the lesions completely regressed in two patients after closure of the protective ileostomy.

Table 1: *Data of literature on operated desmoid tumours in familial adenomatous polyposis*

Author (year)	Jones et al (1986)	Lofti et al (1989)	Penna et al (1993)	Gurbuz et al (1994)	Rodriguez-Bigas et al (1995)	Kadmon et al (1995)	Heiskanen et al (1996)	Soravia et al (2000)	Ho et al (2002)
Paticnts ( )*	29 (8.9)	24 (13)	29 (12)	83 (10)	24 (38)	29 (17)	29(14)	97 (12.4)	11 (1)
Male/Fema e Rati»	7/22	7/17	16/13	36/47	15/9	10/19	12/17	38/59	5/6
Family history	NA	3 (12.5)	NA	49 (59)	NA	3 (10.3)	4 (13.7)	41 (42.2)	NA
Pregnancy	NA	11 (65)	NA	22 (66)	NA	2 (10)	10 (59)	33 (60)	NA
Site	Mesentery 21 Abdominal wall 5 Both sites 4	Mesentery' 24	Mesentery 25 Abdominal wall 4	Abdominal 60 Extra-abdominal 11 Both sites 3 NA 9 (11%)	Mesentery 8 Abdominal wall 5 Both sites 11	Mesentery 19 Abdominal wall 15 Extra-abdominal 2	Mesenterv 15 Abdominal wall 10 Other sites 4	Mesentery 49 Abdominal wall 10, Both sites 31 Extra-abdominal 8	Mesentery 3 Abdominal Wall 4 Both sites 2 Extra-abdominal 2
Mean age at DT occurrence	29.8	34	32	31	28.5	34.5	28	29.9	33
DT development: mean tine from colectomy (yrs)	2	<4	4.9	NA	3.1	NA	3.2	4.6	2.0
Recurrence after surgery	25(85)	24(83)	20(69)	43(68)	20(83)	22(76)	20(69)	77(80)	4(36)

NA = not available

DT = desmoid tumor

** Rate of operated patients*

Table 2: *Chemoprophylaxis of desmoids: personal experience in familial adenomatous polyposis*

TYPE OF LESIONS	Patients	Drug	Duration mean (range) months Months (range)	Length of follow-up mean (range) months	Absence of progression	Regression	Recurrence
DPL	20	Tamoxifen Raloxifen	64 (6-168)	79 (10-168)	19* (95%)	2° (10%)	/
Abdominal wall D	15	Tamoxifen Raloxifen	59 (2-120)	84 (2-154)	13◆ (8.4%)	/	2 (13.3%)

***D**: **D**esmoid; **DPL**: **D**esmoid **P**recursor **L**esion*

° Intraoperative evaluation for second surgery

** No evidence at clinical examination or at*

◆ No evidence of D at clinical examination or at US/CT scan

Radiotheraphy

Radiotherapy is not indicated in the treatment of DTs, because these lesions are relatively insensitive to irradiation and, as a large area would have to be treated, actinic damage of the small bowel is inevitable.

Cytotoxic Chemotherapy

Systemic chemotherapy has been administered to patients with DTs continually growing despite treatment with NSAID or anti-oestrogens or rapidly increasing in size thus leading to life-threatening complications.

However, chemotherapy is rarely employed because of its toxicity. The published reports regard single cases or small numbers of patients. All treated patients were affected with large tumours, had severe symptoms or major complications. The DTs continued to grow even if medically treated and were deemed unresectable. Various types of cytotoxic drugs were adopted.[60-68]

The association with doxorubicin and dacarbazine have generally been chosen in recent years.

More than 50% of the treated patients achieved significant regression of the lesions and some patients were completely cured.

The response to the therapy would appear to last a long time.

It has been noted that this favourable response to chemotherapy of DTs defies the dogma in oncology that low-grade tumours without metastatic potential do not respond to chemotherapy [69]

Table 3: *Drug therapy of desmoids: personal experience in familial adenomatous polyposis*

TYPE OF DESMOIDS	Patients	Drug	Duration Months (range)	Lenght of follow-up Months (range)	Progression (%)	Regression (%)	Stable (%)
Mesentery D	26	Tamoxifen Raloxifen	46 (3-156)	90.5 (3-252)	3◆ (11.5)	21 (80.7)	4 (15.3)
Retroperitoneal fibrosis	6	Tamoxifen Raloxifen	52.5 (18-228)	49.2 (3-224)	1 (16.6)	4 (33.3)	1 (16.6)
Abdominal wall D	19	Tamoxifen Raloxifen	18.4 (1-84)	86.3 (3-224)	2◆ (10.5)	16 (84.2)	1 (5.2)

◆ *Voluntary drop-out in 1 case*

Mesenteric Desmoid and Surgery

The presence of mesenteric DT can be incidentally discovered at the time of total colectomy and can preclude the scheduled procedure on account of technical reasons. In the experience of the Hopital Saint-Antoine of Paris, the presence of mesenteric DT ruled out construction of IPAA (3 patients), conversion of an ileo-rectal anastomosis into an IPAA (3 patients), removal of the rectum for carcinoma (2 patients), construction of a continent ileostomy (2 patients) and duodenal-pancreatic resection (2 patients) [11].

According to Hartley et al.[70], this situation was discovered in 3% of the patients submitted to a first laparotomy and in 30% of those submitted to a second laparotomy, and also influenced the scheduled surgical procedure, generally IPAA. Similarly, Cohen observed significant mesenteric desmoid disease at the time of the attempted IPAA in 7 patients and a definitive ileostomy was necessary [71].

The presence of a fibrous mesenteric mass or a mesenteric fibromatosis may preclude the construction of an IPAA for two reasons: 1) the shortness of the mesentery, 2) the impossibility of folding the ileal loops. In these cases we were able to perform a straight ileo-anal anastomosis since the terminal ileum must not be folded and can be carried down to the anal canal more easily than to the pouch, allowing the ileo-anal anastomosis to be performed without tension.

However, the straight ileo-anal anastomosis has been abandoned on account of the unfavourable functional results. In our experience, multiple longitudinal myotomies of the last 15 cm of ileum provide a satisfactory functional result [72].

Surgical Treatment

For several Authors surgical intervention is the treatment of choice for DTs. A complete excision is recommended because partial excision may trigger a prompt recurrence. However, considering that DTs are basically benign, the advantage of surgery may be weighed with its consequences.

A different approach must be considered for abdominal wall or mesenteric DTs. Common opinion is that abdominal wall DTs can be removed, since the surgical procedure is relatively easy and the possibility of a radical removal is high even in presence of a huge mass. In order to obtain clear margins on histological examination excision in the muscular tissue is recommended, often with the sacrifice of most abdominal wall muscles. It is therefore important to treat DTs when they

are small, otherwise a large musculoaponeurotic defect of the abdominal wall requires reconstruction with synthetic devices or myocutaneous flaps. However, some Authors [13,19,71] maintain that surgery is not advisable even for DTs of the abdominal wall. In fact, the recurrence rate varies from 25 to 100% of cases, even when the DT has been radically resected [11,13,52] and the iterative operation can provoke the development of DT within the mesentery [13-25]. Against imperative surgery, it must be considered that DTs can cease to grow [20] or even regress spontaneously [12,27]. We are in favour of surgery for this type of DT, but believe it necessary to adopt a chemoprevention of the recurrence just after surgery. We treated 15 abdominal wall DTs with radical surgery and employed SERMs as adjuvant therapy in the post-operative period. Recurrence was observed in two patients.

Conversely, mesenteric DTs can be removed only when small and relatively distant from the root of the small bowel mesentery, since there is no plane of cleavage around the mass, enucleation is impossible and a concomitant resection of the surrounding intestinal tract is frequently needed. Otherwise the risk is to remove a large part or the whole of the small bowel. Treatment of intra-abdominal DT is usually reserved to cases in which complications occur, such as small-bowel obstruction, bowel perforation, intestinal bleeding, hydronephrosis or deterioration of the functional results after IPAA. When surgery is chosen with curative intent, radical resection is achieved in about 20% of cases [12,13,30] with a mortality rate ranging from 2 to 10% [12,13,31]. In the other 80% of cases partial resection or biopsy alone with or without intestinal bypass were performed. Severe complications are reported in up to 60% of cases [14]. Short-bowel syndrome, following wide or multiple bowel resections, is reported in 4.7-20% of cases [13,27,31]. Long-term parenteral nutrition and small bowel transplantation can be necessary in some of these patients. The recurrence rate is around 70-80%. The personal attitude was to avoid surgery and treat the lesions medically with SERMs or, in rare cases of refractory response, cytotoxic drugs. In the majority of cases we could arrest the growth of DTs and observe regression of symptoms and mass.

Conclusions

Abdominal wall and mesenteric DTs are a common manifestation in patients with FAP. The natural history is extremely variable and largely depends on the site of DT and its growth rate. Previous abdominal surgery, family history of DTs, *APC* germline mutation distal to codon 1444 and the female gender significantly increase the susceptibility of developing DTs. Prophylactic colectomy may be delayed in women with an attenuated FAP and in patients belonging to a family with evidence of DTs in more than 50% of the members. It seems probable that an attenuated form of mesenteric fibrosis represents the precursor of infiltrating fibromatosis and large mass. Even if the majority of DTs grow slowly and are asymptomatic, a minority of DTs may present a fast increase causing serious compression of intra-abdominal structures and life-threatening complications. In recent years, research has clarified the mechanism of actions of NSAIDs or SERMs and the rationale for their use in DTs. Considering the low toxicity of these drugs they must be considered either as a first-line treatment when a DT or a mesenteric fibromatosis is diagnosed or as a preventive measure when DPLs are discovered at surgery. A close surveillance of the lesions by regular clinical and imaging assessment is mandatory. Progression of the tumour or occurrence of symptoms despite this treatment should promptly indicate cytotoxic chemotherapy. The medical treatment must be

pursued for a long time, since shrinkage of DTs can be delayed by months or even years. However, regression can continue after discontinuation of the therapy. Surgical therapy is indicated when its consequences are not detrimental. Therefore, only extra-abdominal DTs or small mesenteric DTs that are located far from the mesenteric vessels and do not require a large intestinal resection, are susceptible of surgical resection. Post-operative therapy for prevention of recurrence is indicated.

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