Introduction

The term desmoid was first used by Muller [1] to describe the tendon-like aspect and the hard consistency 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 musculoaponeurotic structures predominantly of the abdominal wall (Fig. 1a, b, c) and occasionally of the shoulder girdle, chest wall, inguinal region and extremities. They present as a firm, smooth, painless, progressively growing mass. Imaging investigations are useful in better defining the extent of the tumour which displays an iceberg growth with only a small proportion being clinically manifest. Interestingly, multiple extra-abdominal DTs are frequently discovered in very young patients under the age of 3 [2]. The intra-abdominal DTs develop in the folds of the mesentery or the meso-colon (Fig. 2a, b) even reaching the retroperitoneal tissue or they may grow exclusively in this region. These proliferations are usually single, round or oval in shape and 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

![Fig. 1a. Tc scan revealing a large and invasive desmoid mass arising within the abdominal wall. b Lateral view of the abdomen showing a protruding desmoid mass along the scar of the previous prophylactic colectomy. c Desmoid mass specimen.](image_url)
adenomatous polyps (FAP) patients. This process has been variously referred as mesenteric fibrosis or mesenteric fibromatosis [3-5]. However, whitish, thin plaque-like areas of the mesenteric folds have been frequently identified in FAP patients undergoing laparotomy (Fig. 3a, b). It has been suggested that these mesenteric abnormalities represent precursor lesions of mesenteric fibromatosis and mesenteric DT [6, 7]. 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%. Histology was similar to that of other desmoids [6]. The patients with mesenteric fibromatosis had undergone a significantly higher number of previous abdominal operations than those without [6].

Helical abdominopelvic CT scanning and MRI was employed to characterize and follow up these precursors. It has been suggested that rapidly growing DTs have high signal intensity on T2-weighted images [8]. 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 [7]. Furthermore, CT findings consistent with mesenteric fibromatosis were observed on reviewing the scans of patients subsequently developing DTs [9].

Intra-abdominal DTs can be associated with DTs arising in the abdominal wall. The similarity of intra-abdominal DTs to extra-abdominal DTs is evident in

![Fig. 2a. Intra-operative view shows a precursor desmoid lesion in the fold of the mesentery and b in the mesocolon](image)

![Fig. 3a. Tc scan shows a large desmoid mass arising within the mesentery. b Intra-operative view of desmoid mass](image)
Table 1. Data of literature on operated desmoid tumours in familial adenomatous polyposis

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients ( )</th>
<th>Male/female ratio</th>
<th>Family history</th>
<th>Pregnancy</th>
<th>Site</th>
<th>Mean age at DT occurrence</th>
<th>DT development: mean time from colectomy (years)</th>
<th>Recurrence after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. [14] (1986)</td>
<td>29 (8.9)</td>
<td>7/22</td>
<td>NA</td>
<td>NA</td>
<td>Mesentery 21 Abd. wall 5 Both sites 4</td>
<td>29.8</td>
<td>2</td>
<td>25 (85)</td>
</tr>
<tr>
<td>Gurbuz et al. [2] (1994)</td>
<td>83 (10)</td>
<td>10/19</td>
<td>NA</td>
<td>NA</td>
<td>Abd. 60, Extra- Abd. 11, Both sites 3 NA 9</td>
<td>31</td>
<td>NA</td>
<td>43 (68)</td>
</tr>
<tr>
<td>Rodriguez-Bigas et al. [16] (1994)</td>
<td>24 (38)</td>
<td>12/17</td>
<td>NA</td>
<td>NA</td>
<td>Mesentery 8 Abd. wall 5, Both sites 11</td>
<td>28.5</td>
<td>3.1</td>
<td>20 (83)</td>
</tr>
<tr>
<td>Kadmon et al. [17] (1995)</td>
<td>29 (17)</td>
<td>38/59</td>
<td>NA</td>
<td>NA</td>
<td>Mesentery 19 Abd. wall 15 Extra-abd. 2</td>
<td>34.5</td>
<td>NA</td>
<td>22 (76)</td>
</tr>
<tr>
<td>Heiskanen et al. [18] (1997)</td>
<td>29 (14)</td>
<td>5/6</td>
<td>NA</td>
<td>NA</td>
<td>Mesentery 15 Abd. wall 10, Both sites 4</td>
<td>28</td>
<td>3</td>
<td>20 (69)</td>
</tr>
<tr>
<td>Soravia et al. [19] (2000)</td>
<td>97 (12.4)</td>
<td>41 (42.2)</td>
<td>NA</td>
<td>NA</td>
<td>Mesentery 49 Abd. wall 4</td>
<td>11 (1)</td>
<td></td>
<td>77 (80)</td>
</tr>
</tbody>
</table>

*Rate of operated patients. NA, not available; DT, desmoid tumour; Abd, abdominal

The fact that these growths are histologically identical, they never metastasize and usually occur shortly after an abdominal operation. In the series from the polyposis registries of Denmark and Finland, DTs are located intra-abdominally in 50%, in the abdominal wall in 40% and on the extremities in 10% [10]. While DTs are rare in the general population (two to four 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 [11]. 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 lifetime risk is around 21% [12].

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, 12, 13]. 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.

In our experience, DTs or their precursors such as mesenteric fibromatoses, retroperitoneal fibrosis or simply mesenteric fibrotic thickening have been found in 40 out of the 97 (41.2%) FAP operated patients. Twenty-seven patients (27.8%) developed abdominal wall or mesenteric DTs. The probable explanation of this relatively high frequency of desmoid reaction lies in a more accurate and prospective investigation. (Tables 1 and 2).
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 characterized by an indolent course, rarely by a spontaneous regression and sometimes by an aggressive and rapid growth and a tendency to invade surrounding structures. Desmoid tumours 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 [14, 16]. The consequences of mucosal ischaemia of the small bowel are bleeding or intestinal strictures [21]. Sudden enlargement of the DT can provoke deep vein thrombosis and fatal pulmonary embolism [22]. 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.

Desmoid tumours are the second most common cause of death in FAP patients after colorectal cancer. Intra-abdominal DTs can be responsible for death in up to 11% of FAP patients [23–25]. In the experience of the Johns Hopkins University, the survival rate from DTs evaluated by life-table 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 [26, 27]. The occurrence of small-bowel obstruction or intestinal bleeding in IPAA patients with DTs usually requires the removal of the pouch [21, 26].

Histology

These lesions are typically poorly circumscribed with infiltration of the surrounding soft tissue structures. Histologically, DTs are composed of elongated, uniform, bland fibroblasts and myofibroblasts loosely arranged in sweeping bundles (Fig. 4a, b). Tumour cells are set within a collagensous to myxoid stroma.

Table 2. Desmoids (D), fibromatosis (FB) and desmoid precursor lesions (DPL) in 40 out of 97 FAP patients (personal experience)

<table>
<thead>
<tr>
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<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>19 (9/10)</td>
<td>8 (1/7)</td>
<td>12 (6/6)</td>
<td>7 (4/3)</td>
<td>6 (3/3)</td>
</tr>
</tbody>
</table>

Fig. 4a. Desmoid tumour showing the typical infiltrative growth pattern of the skeletal muscle (original magnification, x50).

[2] The lesion is composed of elongated, spindle-shaped cells with uniform cytological features (original magnification, x200).
causing the lesion to closely resemble normal cellular fibrous tissue or scar. Keloid-like collagen or extensive hyalinization may be present. One of the most characteristic features of DTs is its vascularity with numerous blood vessels showing thick walls and open lumina. Mitotic figures are virtually absent. In fact, the observation of even a few mitotic figures should raise the suspicion of a low-grade fibrosarcoma rather than DTs. On immunohistochemical analysis, tumour cells are generally positive for vimentin and actin. A few cells may also express desmin and S-100 protein. Ultrastructural studies further support the fibroblastic and myofibroblastic nature of DTs.

**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 representative of a clonal population [28]. It has also been shown that the proliferation of desmoid cell cultures is inhibited by the cellular transfection of wild-type APC [29]. The hypothesis has been proposed that DPLs undergo a multi-step process analogous to the cascade suggested for the adenoma-carcinoma sequence developing firstly mesenteric fibromatosis and finally mesenteric DTs [6, 28]. 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.

In the past, several authors found no significant sex differences [2, 30] or a slight prevalence in the female sex, with a female/male ratio of 1.4 [31, 18]. More recently 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 [12, 32].

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 [30, 33, 34], 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 [35]. 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 [35].

**Surgery**

A surgical trauma is generally indicated as a precipitating factor for DT development (Table 3). In particular, in 68–83% of FAP patients, an abdominal operation precedes formation of DTs by a few months up to a few years. The mean time to DT development varies, but it is usually around 2 years [4, 11, 15, 30]. It appears that there is no correlation between the entity of the surgery and the occurrence of DTs. Desmoid tumours affect patients operated by subtotal colectomy and ileo-rectal anastomosis or by restorative proctocolectomy and IPAA in a similar percentage [13, 19, 31, 32], but even a minor abdominal surgical procedure such as appendectomy can induce DTs. Iterative surgery can increase the risk as Penna et al. [13] 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 [11], patients with postoperative DTs had undergone 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 DTs has become clearer when DTs and mesenteric fibromatosis were recog-
nized as stigmata of FAP and a more accurate diagnosis of these complications was achieved. Desmoid tumours have been reported to be frequently associated with Gardner’s syndrome [5]: 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) [2]. Bertario et al. [25] estimated the risk of developing DTs in 897 FAP patients scheduled on the Italian hereditary colorectal tumour registry and found that family history of DTs, osteomas and epidermoid cysts was significantly associated with the presence of the disease. Similarly, Sturt et al. [32] found that family history (especially if more than 50% of the members were affected with DTs) 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. Desmoid tumours will develop when both alleles of the APC gene are faulty, but one of the mutations encompasses the region 3’ of codon 1444 [32, 36, 37]. 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 [38, 39]. An aggressive growth pattern of DTs has been attributed to the presence of a germline APC mutation in codon 1445-1578 [38]. 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 [12]. 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 the 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 [40].

### Desmoid and Oestrogens

#### Mechanism of Action of Oestrogens

The oestrogenic bio-effects are mediated by specific receptor subtypes, ERα and ERβ, which 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), which could be either the steroidal oestrogen, the polyphenolic phyto-oestrogens or the synthetic SERMs (selective estrogen receptor modulators). The latter exhibit either agonist or antagonist oestrogenic actions. The first generation of SERMs are represented by the
triphenylethenes 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-estrogenic effects on the breast and uterus, but an estrogen agonist effect on bone and cardiovascular systems.

The ER expression was shown by the authors both in DT tissues and in desmoid-derived cells in culture [41, 42]. Furthermore, we studied the gene expression of ERs in primary cultures obtained from desmoid tumoral tissue. The results showed that, in all the cultures, ERα and ERβ were variably expressed (Picariello et al., 2006, personal communication); in fact, in some patients the ERα expression was predominant in respect to ERβ. The extremely variable expression of the two ERs in these primary cell cultures underlines the individual differences among patients.

To evaluate if estrogen could influence the DT derived cell growth, primary cell cultures obtained were cultured in presence or in absence of different concentrations of 17βE₂, from 1 pM to 1 μM concentration for 1 week (Fig. 5) [41]. The results showed that 1 nM concentrations of 17βE₂ stimulated cell proliferation in five of the seven cultures analyzed and the effect induced by oestrogen on cell proliferation was different from one cell culture to another. Any influence on cell proliferation by the oestrogen was observed in two of the seven cultures. These results confirmed that oestrogen induced a proliferative effect in the different cell cultures with a cell-specific potency. This could be due to the ER expression pattern and to the different 17βE₂ potency in transactivating gene expression controlled by ERα and ERβ. In those cultures, where the increase of cell growth was great, there was a higher expression of EROβ than ERβ, while in those cultures where the effect of oestrogens was slight or absent, a comparable expression of the two ERs was evident. Therefore, the characteristic pattern of ER expression in each culture could be responsible for the cell culture-specific proliferative potency of 17βE₂, which displays a greater ERα selectivity with a higher potency in transactivating gene expression controlled by ERα rather than ERβ.

We also studied the effect of SERMs on the proliferation of desmoid cell cultures and the putative mechanism of action of SERMs. Firstly, we observed that tamoxifen inhibited the proliferative effect of 17βE₂ [41]. Subsequently, we cultured desmoid cells in the presence of different concentrations of an analogue of raloxifene, LY117018 for one week (Fig. 6) [42]. LY117018 induced a dose-dependent inhibition of cell proliferation at the pharmacological dose of 5 μM concentration independently of a greater or lesser expression of each ER. This suggests that pharmacological concentration of raloxifene, as well as other SERM molecules (e.g. tamoxifen and toremifene), could directly inhibit the proliferation and function of DT cells acting through or independently of ERs. To investigate if the inhibition of cell proliferation by LY117018 was dependent on the apoptotic cell death process, the desmoid cells were stimulated with the drug and then the internucleosomal fragmentation of genomic DNA was evaluated. The results showed that DT derived cell cultures stimulated with 5 μM of raloxifene did not develop the typical nucleosomal ladder pattern of DNA degradation, clearly exhibited by the positive control (HL-60 cells stimulated for 4 h with 2.5 μg/ml camptothecin; personal observations). These data suggest

![Fig. 5. Effects of 17βE₂ on cell growth of desmoid tumour cells. Cells were plated in phenol-red-free growth medium supplemented with 1% charcoal stripped foetal calf serum, containing different concentrations of 17βE₂. After 1 week cells were counted. Results were expressed as % of control values of three separate experiments. *p<0.05](image-url)
that the biological effect exerted by SERM molecules on DTs is mediated only in part by their binding to both ERα and ERβ, but is essentially due to a cytotoxic and cytostatic mechanism. The hypothesis to be evaluated is that raloxifene as well as triphenylethenes reduce the synthesis of TGFβ1, a potent growth stimulator of mesenchymal cells. Recent studies have shown increased 17βE, production, 17βE, mRNA expression and 17βE, receptor number in desmoid cells in culture compared with normal fibroblasts [43]. This growth factor enhances organic macromolecule accumulation in the extra-cellular matrix (ECM) via a reduction of matrix metalloproteinases (MMPs), a family of zinc-dependent neutral endopeptidases which are involved in the degradation of ECM, and an increase in the natural tissue inhibitors of MMPs. The growth of DTs is favoured by a decreased collagen degradation rather than by an increase of collagen synthesis. It has been shown that the presence of 1 μM toremifene in the cultural medium inhibited 17βE, activity and consequently reduced collagen accumulation by increasing collagen degradation.

**Treatment with SERMs**

Anti-oestrogen therapy has been largely based on triphenylethenes such as tamoxifen or its chlorinated derivate toremifene since its first use by Waddell in 1983 [44]. 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 [45]. 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 tamoxifen (120–200 mg/day) obtaining a cessation of growth in 63–77% of the patients [42, 47]. 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 [46]. However, the risk of endometrial cancer with 20 mg per day of tamoxifen has been recognized for many years [48, 49]. Conversely, lack of worrying endometrial stimulation seen with triphenylethenes 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 five cases and partial remission in five other cases [50]. 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. Tables 4 and 5 focuses our personal experience respectively on chemoprophylaxis and on drug therapy.
**Mechanism of Action of NSAIDs**

Several reviews [51–53] have summarized the intriguing and accumulating evidence that non-steroidal anti-inflammatory drugs (NSAIDs) have potential as anti-cancer drugs. NSAIDs have been shown experimentally to stimulate apoptosis and to inhibit angiogenesis, two mechanisms that help to suppress malignant transformation and tumour growth.

The mechanism of action common to NSAIDs is the inhibition of cyclooxygenase (COX) enzymatic conversion of the polyunsaturated fatty acid arachidonic acid (produced by the hydrolysis of phospholipids catalyzed by phospholipase A) to prostaglandin G, (PGG₂) [56]. PGG₂ is converted to prostaglandin H₂ by the peroxidase activity of the COX enzyme, and then PGH₂ may be converted by tissue-specific isomerases to one of the five biologically active prostanoids: PGE₂, prostaglandin D₂, prostaglandin F₂α, prostacyclin or thromboxane [57].

Two distinct isoforms of COX, designed COX-1 and COX-2 have been recognized [58, 59]. COX-1 is expressed constitutively in the human kidney and brain, its expression is induced in many tissues during inflammation, wound healing and neoplasia [58–59]. Although COX-2 is expressed constitutively in the human kidney and brain, its expression is induced in many tissues during inflammation, wound healing and neoplasia.

NSAIDs vary in their abilities to inhibit COX-1 or COX-2 at different concentrations and in different tissues [60, 61]. Aspirin is the only NSAID known to react covalently with COX-1 and COX-2 by selective acetylation of a specific serine residue at position 529 and 516, respectively [62, 63]. Aspirin acetylation of COX-1 results in a complete blockade of arachidonic oxidation to PGH₂, aspirin has thus been report-

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**Table 4. Chemoprophylaxis of desmoids: personal experience in familial adenomatous polyposis**

<table>
<thead>
<tr>
<th>Type of lesions</th>
<th>Patients</th>
<th>Drug</th>
<th>Duration, mean range (months)</th>
<th>Length of follow-up mean range (months)</th>
<th>Absence of progression</th>
<th>Regression</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPL</td>
<td>20</td>
<td>Tamoxifen/raloxifen</td>
<td>65 (6–168)</td>
<td>79 (10–168)</td>
<td>18</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Abdominal wall D</td>
<td>15</td>
<td>Tamoxifen/raloxifen</td>
<td>59 (2–120)</td>
<td>84 (2–154)</td>
<td>13</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

_D, Desmoid; DPL, Desmoid precursor lesion_

'Intraoperative evaluation for second surgery; 'No evidence at clinical examination or at CT scan; 'No evidence of D at clinical examination or at US/CT scan

**Table 5. Drug therapy of desmoids: personal experience in familial adenomatous polyposis**

<table>
<thead>
<tr>
<th>Type of desmoids</th>
<th>Patients</th>
<th>Drug</th>
<th>Duration months (range)</th>
<th>Length of follow-up months (range)</th>
<th>Progression</th>
<th>Regression</th>
<th>Stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesentery D</td>
<td>8</td>
<td>Tamoxifen/Raloxifen</td>
<td>65 (2–156)</td>
<td>57 (2–156)</td>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis</td>
<td>1</td>
<td>Tamoxifen/Raloxifen</td>
<td>24 (2–48)</td>
<td>24 (2–192)</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal wall D</td>
<td>2</td>
<td>Tamoxifen/Raloxifen</td>
<td>14 (2–44)</td>
<td>14 (2–60)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Voluntary drop-out in one case*
ed to be a more potent suppressor of PGH₂ formation by the activity of COX-1 than that formed by COX-2 [64]. The other NSAIDs such as ibuprofen and indomethacin, produce reversible or irreversible inhibition of both COX-1 and COX-2 by competing with the arachidonic acid for the active site of the enzyme [56].

Although NSAIDs are widely used and are effective, their long-term use is limited by gastrointestinal effects such as dyspepsia and abdominal pain, gastric and duodenal perforation or bleeding, and small bowel and colonic ulcerations. The discovery of COX-1 and COX-2 has led to the suggestion that the therapeutic effect of NSAIDs is primarily the result of inhibition of COX-2, whereas the toxicity of NSAIDs may primarily result from inhibition of COX-1 [65]. In fact, NSAIDs toxicity in the gastrointestinal mucosa is the result of inhibition of COX-1 activity in platelets, which increases the tendency of bleeding, and in gastric mucosa, where prostanoids play an important role in protecting the stomach from erosion and ulceration [55]. While the conventional NSAIDs inhibit COX-1 and COX-2 to the same extent, the development of a new group of anti-inflammatory drugs, the coxibs, selective inhibitors of COX-2 (e.g., celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib), represent a response to the unsatisfactory therapeutic profile of NSAIDs and it was hoped that coxibs would be better tolerated than non-selective NSAIDs and would be equally efficacious and that selective inhibition of COX-2 could be an effective strategy for preventing cancer.

Several prostaglandins such as PGE₂, suppress immunosurveillance through down-regulation of lymphokines, T-cell and B-cell proliferation, cytotoxic activity of natural killer cells and secretion of TNFα and interleukin 10 [66]. It has been shown that there is a close relationship between PGE₂ and EGF-receptor signalling systems. PGE₂ induces the activation of metalloproteinases MMP2 and MMP9, increases expression of TGFβ, transactivates EGF receptor, and triggers mitogenic signalling in gastric epithelial and colon cancer cells as well as in rat gastric mucosa in vivo. This mechanism may explain how PGE₂ exerts its trophic action on gastric and intestinal mucosa, resulting in hypertrophy and cancer. The inhibition of prostaglandin synthesis by NSAIDs can explain the anti-tumoral effect of these drugs.

Despite continuing uncertainty about the molecular pathways by which NSAIDs may inhibit neoplasia, there is mounting evidence that tumour inhibition, for example in colorectal cancer, may be mediated by at least two distinct cellular processes: the ability of NSAIDs to restore apoptosis in APC-deficient cells [67, 68] and their capacity, particularly in the case of coxibs, to inhibit angiogenesis. Apoptosis, or programmed cell death is needed to maintain homeostasis in continuously replicating tissues such as intestinal mucosa [69]. The suppression of apoptosis allows APC-deficient cells to accumulate and form adenomatous polyps. Further suppression of apoptosis occurs as these cells develop additional genetic mutations and phenotypic changes [70]. In Vitro, both non-selective NSAIDs and selective COX-2 inhibitors stimulate apoptosis in APC-deficient colonic cells that have not undergone malignant transformation [71]. Non-selective NSAIDs lose their ability to inhibit chemically induced tumours when polyps undergo malignant transformation. In contrast, selective COX-2 inhibitors stimulate apoptosis and suppress growth in many carcinomas, including cultured human cancers of the stomach, oesophagus, tongue, brain, lung and pancreas [72–77]. The precise mechanism by which NSAIDs restore apoptosis remains controversial [78], but treatment of colorectal carcinoma cells with NSAIDs or coxibs increases the concentration of arachidonic acid that, if unesterified, modulates mitochondrial permeability and causes release of cytochrome C, thus leading to apoptosis [79].

Other experimental models suggest that NSAIDs induce apoptosis by either COX dependent or COX independent mechanisms. In the latter case, the G0/G1 cell-cycle block caused by celecoxib in colon cancer cell lines and In Vivo models is related to a decreased expression of cyclins A and B1, and to the expression of cell-cycle inhibitory proteins p21WAF1 and p27KIP1 [80] as well as the coxib NS-398 enhanced apoptosis in cells which do not express COX-2 enzyme [78]. NSAIDs have also been reported to induce apoptosis through 15-lipoxygenase-1, independent of COX-2 [81]. However, many of these effects have been demonstrated only with high concentrations of NSAIDs In Vitro and are of uncertain clinical relevance.

Several studies have shown a relation between angiogenesis and COX-2 expression [82], so a second cellular process by which NSAIDs and in particular COX-2 inhibitors may inhibit tumour growth is through inhibition of angiogenesis and neovascularization [83]. COX-2 induces proangiogenic factors such as VEGF, inducible nitric oxide synthase, interleukins 6 and 8, and TIE, [83, 84], and it produces prostaglandins that have both autocrine and paracrine effects on proliferation and migration of endothelial cells In Vitro [82, 85]. COX-2 is overexpressed in “activated” tumour endothelial cells, whereas COX1 is expressed in normal endothelial cells [82]. COX-2 derived prostaglandins stimulate angiogenesis In Vivo, and COX-2 inhibition of endothelial cells slows down tumour growth. In par-
ticular, COX-2 modulates the production of angiogenic factors by tumour cells, whereas COX-1 regulates angiogenesis of endothelial cells in normal tissue [83]. Therefore the hypothesized mechanism by which NSAIDs block angiogenesis is the inhibition of COX-1 and COX-2 activity in endothelial cells. Other studies supported these data also in In Vivo models, focusing on the role of celecoxib in inhibiting of blood vessel formation, tumour growth and development of metastasis [86]. In contrast, toxic concentrations of aspirin or indomethacin are required to block vascular endothelial tube formation [83, 87]. These experiments suggest that COX-2 may be essential for tumour vascularization and growth.

Finally, Brueggemeier et al. [88] showed co-expression of the aromatase enzyme and COX-2 in human breast cancer, with a significant association with gene expression of both: Thus, COX-2 may be the cause of progression of oestrogen-dependent breast cancer by autocrine and paracrine mechanisms, by direct stimulation of tumour cell proliferation, or by indirect upregulation of aromatase activity [88].

**Treatment with NSAIDs**

The fact that both β-catenin and mutated APC are implicated in colon cancer and DT development [89, 100] and that prostaglandins and cyclooxygenase have a role in colonic neoplasia and FAP progression [68, 91–93], has prompted 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 generalized 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., 2006, personal communication). 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 [94], 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, D FU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(SH)-furon), blocks the cellular growth, but does not promote apoptosis, suggesting that regulation of apoptosis does not play a major role in this neoplasm [95] 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 a few patients was a complete regression obtained [87, 96–97]. This treatment seems less efficacious in patients undergoing partial resection of their DT prior to medical therapy [19]. Most responses were observed after a 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 tamoxifen, 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 [22]. As anti-cancer 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 to in the literature and the absence of prospective randomized trials makes estimation of the effect of NSAIDs difficult, they can be effective in controlling 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 [98], interferon-α-2b, progesterone, prednisolone, ascorbic acid, testosterone, analogues of LHRH, and pirfenidone [99–102]. Recently, imatinib mesylate has been shown to be active in two patients not affected by FAP 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 [103]. These data must be confirmed on DTs in association with FAP and on a larger series.

Prevention of Desmoid Tumours

Chemoprophylaxis 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 DTs 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 Tables 4 and 5. 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 6. Results of chemotherapy for mesenteric desmoid

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of chemotherapy</th>
<th>Desmoid numbers</th>
<th>Partial response &gt;50%</th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsukada et al. 1991</td>
<td>Vincristine, cyclophosphamide, doxorubicin, 5-FU</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Patel et al. 1992</td>
<td>Doxorubicin, dacarbazine</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lynch et al. 1994</td>
<td>Doxorubicin, dacarbazine</td>
<td>2</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Schnitzler et al. 1997</td>
<td>Doxorubicin, dacarbazine</td>
<td>5</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Risum and Bulow 2003</td>
<td>Doxorubicin</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Okuno and Edmonson 2003</td>
<td>Ifosfamide, etoposide, mitomycin, doxorubicin, Cis.</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Kono et al. 2004</td>
<td>Vinblastine, methotrexate</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

Radiotherapy

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 NSAIDs 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 [104–112]. The association with doxorubicin and dacarbazine have generally been chosen in recent years (Table 6). 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 [113].

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 Saint-Antoine Hospital of Paris, the presence of mesenteric DT ruled out construction of IPAA (three patients), conversion of an ileo-rectal anastomosis into an IPAA (three patients), removal of the rectum for carcinoma (two patients), construction of a continent ileostomy (two patients) and duodenal-pancreatic resection (two patients) [13]. According to Hartley et al. [113], 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 seven patients and a definitive ileostomy was necessary [114].

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 [115].

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 [16, 26, 114] 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 [13, 15, 87] and the iterative operation can provoke the development of DT within the mesentery [18, 21–31]. Against imperative surgery, it must be considered that DTs can cease to grow [27] or even regress spontaneously [14, 33]. 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 postoperative 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 DTs 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 [14–16] with a mortality rate ranging from 2 to 10% [14, 19, 21]. 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 [19, 21, 34]. Long-term parenteral nutrition and small-bowel transplantation can be necessary in some of these patients. The recurrence rate is around 70–80% (Table 3). 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 hi-
tory 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. Postoperative therapy for prevention of recurrence is indicated.

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Desmoid Tumours in Familial Adenomatous Polyposis


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