Noncytotoxic Drug Therapy for Intra-Abdominal Desmoid Tumor in Patients with Familial Adenomatous Polyposis

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Forty of 416 patients with familial adenomatous polyposis were noted to have intra-abdominal desmoid tumors, and a subgroup of 16 were treated with noncytotoxic drug therapy. Drugs used were sulindac (14 patients), sulindac plus tamoxifen (3 patients), indomethacin (4 patients), tamoxifen (4 patients), progesterone (DEPO-PROVERA®; Upjohn Co., Kalamazoo, MI) (2 patients), and testolactone (1 patient). Therapy with these drugs for continuous periods of six months or more resulted in three complete and seven partial remissions. When treated patients were compared with untreated patients (n = 12), there were significant benefits for the treated group, both in reduction of desmoid size and in improvement of symptoms, despite the inherent selection bias against this. Sulindac was the only drug used in enough patients to permit independent evaluation of its effect, with one complete and seven partial reductions of tumor size. Some patients had a delayed response to sulindac, with tumor shrinkage occurring after an initial period of tumor enlargement. When using sulindac for the treatment of desmoid tumors, this phenomenon should be considered. [Key words: Intra-abdominal desmoid tumor; Familial adenomatous polyposis; Nonsteroidal anti-inflammatory drugs; Antiestrogen drugs; Prostaglandin synthesis]

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Familial adenomatous polyposis (FAP) is a hereditary disease with an autosomal dominant pattern of inheritance. Patients with FAP will invariably develop large bowel cancer unless prophylactic colectomy is carried out. Various extracolonic manifestations of the inherited growth disorder represented in FAP have been reported.[1–5] Desmoid tumors and periampullary carcinoma are two of the most fatal extracolonic manifestations and usually occur in patients who have avoided the risk of large intestinal cancer by having the large bowel removed.[6] Desmoid tumors are locally infiltrative overgrowths of fibrous tissue that occur in musculoaponeurotic tissues. Although extra-abdominal and abdominal wall desmoids can occur, it is the intra-abdominal, and in particular the mesenteric, desmoid tumor that causes problems of management in patients with FAP.

The incidence of desmoid tumors in the general population is very low (2–4 cases per 106 per year),[7] but desmoid tumors develop in a relatively high percentage of patients with FAP (10–18 percent), especially in that subset of patients who also display the extracolonic manifestations defined in Gardner's syndrome.[2, 5, 7–9] Desmoid tumors are predominantly found in premenopausal women and, in 80 percent or more of the patients, develop following colectomy.[5, 8, 10] When small, desmoid tumors may be asymptomatic, but, as they enlarge, they may cause symptoms of abdominal pain, nausea, vomiting, and ureteral obstruction. Surgical cure of intra-abdominal desmoids is rare because of the difficulty of complete excision. An alternative treatment is the use of nonsteroidal anti-inflammatory drugs or antiestrogen drugs. Previous reports have included some promising results, but

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most series have small numbers of cases.[5, 10–15] In this study, we have reviewed the outcome of a relatively large series of FAP patients treated for intra-abdominal desmoid tumor by noncytotoxic drugs, to better define the role of these drugs in the treatment of this condition.

MATERIALS AND METHODS

Four hundred sixteen patients diagnosed as having FAP were entered into the Familial Polyposis Registry established at the Cleveland Clinic Foundation in 1979. Forty-two of these patients were noted to have one or more desmoid tumors. Forty of the 42 patients had intra-abdominal desmoid tumors. These form the study population.

Twelve patients were followed for periods of at least six months without any specific antidesmoid therapy, and they form a nonrandomized, historic control group. They are compared with 16 patients whose desmoid tumors were treated with noncytotoxic drugs for one or more uninterrupted periods of at least six months. Four patients had desmoid tumors that were initially observed for at least six months and then treated. They have been included in both groups. Twenty-one of the 24 intra-abdominal desmoid tumors were diagnosed histologically, and three tumors were diagnosed clinically.

A total of 28 periods of drug treatment were available for evaluation. Drugs used included sulindac alone (n = 14), sulindac plus tamoxifen (n = 3), indomethacin (n = 4), tamoxifen (n = 4), progesterone (DEPO-PROVERA®) (n = 2), and testolactone (n = 1). The dosages of sulindac ranged from 300 to 450 mg/day (median dose, 300 mg/day), of tamoxifen from 10 to 40 mg/day (median, 20 mg/day), and of indomethacin from 75 to 150 mg/day (median, 75 mg/day).

Any patients who received noncytotoxic chemotherapy after prior excisional surgery, radiotherapy, or cytotoxic chemotherapy were excluded from the study.

The endpoints of the study were desmoid size and symptoms attributable to the tumor. Tumor size was measured by CT scan and/or by clinical examination. The tumor was measured first along its longest axis and again along the axis perpendicular to this axis. If the desmoid tumor disappeared, the result was defined as a "complete remission". If the tumor size decreased 50 percent or more in two axes or 30 percent or more in one, the result was termed "partial remission". If the tumor size decreased less than 50 percent in two axes or less than 30 percent in one, or if it increased less than 25 percent, the result was defined as "no change". If the tumor size increased 25 percent or more in either one or two axes, or if another desmoid tumor was noted, this result was designated "progression of disease".

The severity of symptoms was determined by patient history. Patients were asked to evaluate abdominal pain as "better", "same", or "worse". Symptoms likely to be due to other diseases (*e.g.*, ureteral calculi) were excluded from analysis.

Patients were followed at six monthly intervals, according to the protocol set out in the Cleveland Clinic Familial Polyposis Registry for patients with intra-abdominal desmoid tumors. At each visit, patients had an interview with one of the authors, including an abdominal and, where appropriate, proctoscopic examination. CT scans were usually performed at this time. On occasion, CT scans were performed at outside institutions, and all scans were reviewed by one of the authors (C.R.G.) in a blinded fashion. No assessment of patient compliance in taking the drugs prescribed was possible.

Data are expressed as mean and standard deviation. Fisher's exact test and the Mann-Whitney U test were used for statistical analysis.

RESULTS

Three patients in the control group died of causes related to the desmoid tumor. There were no deaths in the treatment group. Table 1 shows the basic demographic data for the two groups. In both, there is the expected female predominance, while the earlier onset of desmoid tumors in the treatment group suggests a more aggressive form of disease in these patients. Initial surgery for FAP included total abdominal colectomy with ileorectal anastomosis (control = 5, treatment = 8), total proctocolectomy with ileostomy (control = 4, treatment = 3), and total proctocolectomy with ileoanal pouch anastomosis (control = 0, treatment = 3).

The symptoms caused by desmoid tumors and their initial size as determined by CT scan are presented in Table 2. Measurement of size was possible in only 5 of the control group and in 14 of the treatment group, both groups displaying a large variation. The difference in mean tumor size between groups is not significant, although there is a trend in favor of larger tumors in the treatment

Table 1.
Basic Data

	Control	Treatment
Sex (M:F)	2:10	4:12
Age at operation for FAP (yr)	21.3 ± 9.2	26.1 ± 8.6
Age at desmoid diagnosis (yr)	28.0 ± 10.5	29.4 ± 10.4
Time from operation to desmoid (yr)	6.7 ± 4.6	3.3 ± 4.0*
Length of follow-up (months)	60.5 ± 42.5	42.8 ± 21.3

* $P < 0.05$, control *vs.* treatment, Mann-Whitney U test.

Table 2.
Initial Tumor Size and Patient Symptoms

	Control	Treatment
Size (cm)	10.3 ± 10.5	14.6 ± 8.1
Palpable mass (n)	7	14*
Pain	5	7
Partial bowel obstruction	5	4

* $P < 0.05$, control *vs.* treatment, Fisher's exact test.

Table 3.
Response to Treatment, Size

	Control	All Drugs	Sulindac Only
Complete remission	1	3	1
Partial remission	1	8	7
No change	3	2	4
Progression of disease	7	3	2
Any remission	2	11*	8†
No remission	10	5	6

* $P < 0.002$, control *vs.* all drugs.
† $P < 0.05$, control *vs.* sulindac alone.

Table 4.
Response to Treatment, Symptoms

	Control	All Drugs	Sulindac Only
No. with pain	5	7	6
Pain better	0	5*	4†
Pain unchanged or worse	5	2	2

* $P < 0.03$, control *vs.* all drugs.
† $P < 0.05$, control *vs.* sulindac alone.

group. This group also had a greater proportion of tumors that were palpable, although the number of patients who complained of pain or symptoms suggestive of small bowel obstruction in the treatment group was not different from that in the control group.

Tables 3 and 4 show the natural history of the untreated desmoid tumors and the results of drug treatment in the other group, combining all drugs and then analyzing the results of treatment with sulindac alone. The numbers of patients being treated with the other medications are too small for subgroup analysis. However, all three patients receiving progesterone or testolactone had some decrease in size of tumors, two with a partial remission and one with a complete remission. Tamoxifen achieved one partial remission and one no change, and one tumor increased in size. Treatment with indomethacin resulted in one complete remission and one no change, and two tumors increased in size.

Of the eight patients treated with sulindac who had a decrease in tumor size, this decrease was evident a mean of 8.0 (± 4.3) months after the start of treatment in three patients and 24.3 (± 8.8) months later in five patients. In this latter, delayed-response group, tumor size initially increased and then started to decrease later.

Because of the difficulty of defining symptoms, we have used pain as the sole indicator of symptomatic relief in our patients. The results can be seen in Table 4. Less than 50 percent of each group had pain initially, but the treatment group received a significant benefit from therapy. Both patients receiving progesterone and testolactone noted a decrease in pain, while the two patients who had pain on presentation and received tamoxifen noted no change in symptoms with treatment.

Sulindac therapy was associated with side effects in four patients (29 percent). These included gastrointestinal bleeding (two cases), gastric ulcer (one case), and nausea and vomiting (one case). Cimetidine or ranitidine was used in two patients to control side effects, enabling treatment with sulindac to continue. In two patients, sulindac was discontinued, tamoxifen being used in one.

DISCUSSION

The results of this retrospective, nonrandomized study of noncytotoxic drug therapy in FAP patients show that such therapy can be effective in reducing tumor size and the severity of symptoms associated with intra-abdominal desmoid tumors. The analysis of untreated patients shows that desmoid tumors tend to increase in size if left alone but that spontaneous regression can occur. The incidence of this in our series was 17 percent (2/12). Others have

also reported spontaneous regression in small numbers of cases.[9, 16, 17] The design of the study leads to selection bias, with more symptomatic, larger, and more quickly growing tumors being treated, while the less aggressive tumors are the ones observed. In addition, the small numbers of patients being treated with some drugs make evaluation of the effects of these drugs difficult. Despite these problems, a benefit for drug therapy has been demonstrated.

The options for treating intra-abdominal desmoid tumors include surgery, irradiation, and both cytotoxic and noncytotoxic chemotherapy. Our experience of surgical therapy is being reported separately, but others have found complete excision difficult and recurrences common.[10] It is important to distinguish intra-abdominal and mesenteric desmoid tumors from body wall tumors when evaluating the results of surgery, since the latter group, by its nature, is easier to resect and usually less symptomatic. Radiotherapy and cytotoxic chemotherapy are also ineffective and, in our experience, associated with a high death rate.[18]

Noncytotoxic chemotherapy has traditionally been with either nonsteroidal anti-inflammatory agents (NSAIDs) or hormonal manipulation. NSAIDs are inhibitors of prostaglandin synthesis,[13, 19-21] and tumor cells tend to produce excessive amounts of prostaglandins.[20] Prostaglandin, a potent suppressor of both monocyte antigen-presenting function and T cell expression of interleukin-2,[22, 23] is immunosuppressive,[14, 24] and so inhibition of prostaglandin synthesis may act to block the immunosuppression and retard tumor growth.[13] Severe injury is known both to induce increased suppressor T cell activity and to increase tumor weight and volume,[21, 22] possibly explaining the tendency for desmoid tumors to appear after major abdominal surgery. This surgically enhanced tumor growth can be inhibited by NSAIDs.[21] Prostaglandins also have roles in the stimulation of cyclic AMP synthesis[13, 24] and have been shown to inhibit induction of ornithine decarboxylase, a property associated with tumor suppression.[25] Therefore, their mechanism of action in desmoid inhibition may be a combination of a biochemical effect on tumor growth and a reduction in immune suppression, both mediated by antiprostaglandin activity.

Desmoid tumors are more common in women and enlarge with pregnancy or with birth control pills.[4, 5, 14] This is suggestive of a hormonal influence on desmoid growth.[11, 14] Estrogen receptors have been found in 33 to 75 percent of the desmoid tumors,[14, 26] and tamoxifen, an antiestrogen drug, also inhibits prostaglandin synthesis.[12] Reports to date have shown some effect of tamoxifen in some patients, although patient numbers are limited to two or three cases per report.[11, 13, 15] Toremifene, a tamoxifen analog, has apparently produced drastic regression of desmoid tumors in some patients, although detailed data on this study are unpublished.[27]

The delayed response seen in some of our patients treated with sulindac is an important phenomenon, since it means that the full effect of treatment cannot be determined with follow-up of less than two years. The mechanism of such a phenomenon is not clear, although it may be that antiprostaglandin treatment is not effective until a critical tumor mass is present.

The gastrointestinal side effects noted in this study are well known to be associated with NSAIDs, and in two cases they responded to dose reduction and to the addition of an H_2 receptor blocking drug. Histamine is an activator of suppressor cells, and the blockade of H_2 histamine receptors enhances immunologic response.[13] Therefore, there is a theoretical advantage for H_2 receptor blockade in the treatment of desmoid tumors. According to Flower[19] and Ferreira and Vane,[28] the concentrations of NSAIDs required to inhibit prostaglandin synthesis are generally much lower than normal therapeutic doses, a factor which may enable dose reduction in desmoid patients to reduce the incidence of side effects.

We recommend that sulindac, given in a relatively low dose for an extended period of time with or without H_2 receptor blockade, should be the first choice of treatment for intra-abdominal desmoid tumors in patients with FAP. Such therapy should be continued for at least two years despite an apparent lack of early response, unless worsening symptoms mandate surgery or the addition of other treatment modalities. For female patients, tamoxifen may be used, and, in male patients intolerant of NSAIDs, progesterone (DEPO-PROVERA®) or testolactone may have some effect. These agents may be added to sulindac if no response to that drug alone is observed. In patients intolerant of sulindac, other NSAIDs may be substituted. Surgery should be reserved for specific indications, such as relief of intestinal or urinary tract obstruction.

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