Int J Colorect Dis (1989) 4:30–36

International Journal of Colorectal Disease

Original articles

Mesenteric fibromatosis complicating familial adenomatous polyposis: predisposing factors and results of treatment*

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Abstract. Between January 1975 and December 1983, 24 of 183 patients (13%) with familial adenomatous polyposis (FAP) seen at the Mayo Clinic had mesenteric fibromatosis (MF). MF was found most often in FAP patients with associated extracolonic "Gardner" signs (19 patients) and those who had had previous abdominal surgery (20 patients). In 4 patients, MF appeared spontaneously. The male-to-female ratio was 0.4, with a median age of 31 years in women and 37 years in men. Ten of 24 patients (42%) had been asymptomatic prior to diagnosis at time of surgery for FAP. Complications of the disease included intestinal or urinary tract obstruction. Minimal surgical manipulation seemed to be associated with fewer postoperative complications and a lesser risk of regrowth of the tumor. Nonsurgical treatment, including tamoxifen and sulindac in combination, may be beneficial. Surgery should be reserved for relief of obstruction, and bypass is preferred to resection.

Mesenteric fibromatosis (MF) is a proliferation of fibroblasts in the mesentery, where they form a mass. Such a mass may be well-defined, it may be encapsulated, or it may be totally unencapsulated and irregular. In the last case, the periphery of the mass will have the appearance of infiltration. This gives rise to the adjective "aggressive" in describing some forms of fibromatosis. The fibroblastic proliferation has a moderate degree of cellularity, and mitoses are infrequent. There is, in addition, a tendency to form vascular channels. When fibromatosis is associated with hyalinization, a manifestation of collagen production, the lesion is very firm to palpation and is referred to as a "desmoid tumor" or, more properly, "fibromatosis of desmoid type." Fibromatosis is a relatively pure proliferation of fibroblasts. Although some vascular spaces may be present, other cellular elements are usually lacking. These features separate MF from retroperitoneal fibrosis, in which fibroblastic proliferation and hyalinization also occur. Moreover, in retroperitoneal fibrosis, chronic inflammatory cells, often in a perivascular location, are a part of the fibroinflammatory process.

Fibromatosis of the mesenteric or the desmoid type is seen almost exclusively in patients with familial adenomatous polyposis (FAP). Many physicians believe it occurs more frequently in patients with FAP who have other extracolonic lesions, the so-called "Gardner syndrome" (GS). The purposes of our investigation were to assess the frequency of MF in our patients with FAP; to identify possible factors that may predispose to MF; to characterize the clinical and biological behavior of FAP; and, finally, to evaluate the clinical response of FAP to various forms of treatment.

Patients and methods

During the 9 years between January 1975 and December 1983, 183 patients with FAP were seen at the Mayo Clinic. The present investigation was based on a retrospective review of their medical records. In 68 of these patients (37%), extracolonic "Gardner" signs were recorded. In the remaining patients, extracolonic signs were not recorded. Twenty-four of the 183 patients (13%) had well-documented evidence of MF. This diagnosis was based on the history and physical examinations, supplemented by one or more of the following investigations: ultrasonography, computed axial tomography, excretory urography, and angiography. In 23 of the 24 patients, the diagnosis was

* Presented in part at the Annual Meeting of the American Society of Colon and Rectal Surgeons, San Diego, California, USA, May 5 to 10, 1985

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confirmed by direct observation during abdominal operations and by the microscopic examination of specimens removed during the operation.

FAP was diagnosed only in patients who had innumerable adenomatous polyps diffusely distributed throughout the colon and rectum. The extracolonic "Gardner signs" included epidermoid cysts, osteomas, keloid, extra teeth, adenomatous polyps or carcinoma in the duodenum or small intestine, and papillary carcinoma of the thyroid. For the purposes of this report, those patients in whom the only extracolonic manifestation was MF were classified as having FAP; those with other extracolonic manifestations were classified as having GS.

Results

Predisposing factors

Extracolonic signs. MF was found more often in patients classified as having GS (19/68, 28%) than in those with FAP (5/115, 4.3%).

Previous abdominal surgery. Twenty of the 24 patients (83%) had had a total abdominal colectomy before the diagnosis of MF was made. None of those patients had evidence of MF at the time of the colectomy. Four of those patients had had other intra-abdominal surgical procedures 2 to 22 years before the colectomy. In the remaining 4 patients (17%), the MF seemed to have developed "spontaneously": they had had neither intra-abdominal operations nor recognized blunt trauma to the abdomen before the diagnosis of MF. In the 20 patients who had had previous colectomies, 1 to 28 years had elapsed between the time of the operation and the diagnosis of MF. In most patients (75%), MF was diagnosed within the first 4 years after the colectomy.

Sex. In the total sample of 183 patients, 90 were women and 93 were men (male:female ratio approximately 1). In the 68 patients with GS, 38 were women and 30 were men (sex ratio 0.8). Of the 24 patients with MF, 17 were women and 7 were men (sex ratio 0.4).

Age. The median age at the time of diagnosis of MF was 31 years (range 20 to 47 years) in women and 37 years (range 23 to 60 years) in men. The age at onset is probably related to the age at which the colectomy was done. In all the female patients, the MF appeared before menopause.

Pregnancy. Six of the 17 women with MF had never been pregnant before the diagnosis of MF was made; the other 11 had had 1 or more pregnancies.

Family history. Three of the 24 patients with MF had at least one other relative with MF (a parent in 1 case and a sibling in the other 2). Those three affected relatives had FAP as well as MF.

Extramesenteric fibromatosis. In 6 of the 24 patients with MF (25%), fibromatosis-like lesions developed in extramesenteric locations, including keloid in the abdominal scar (3 patients), desmoid of the chest wall (2 patients), and desmoid of the back and gluteal region (1 patient).

Preoperative findings

In 10 of the 24 patients (42%), the MF had been totally asymptomatic before it was diagnosed during intra-abdominal surgery for FAP. Five of those patients have remained asymptomatic for 1 to 2 years since the operation. In the other 5 patients, symptoms developed later in the course of the disease. Fourteen of the patients (58%) had had preoperative symptoms, mostly due to the intra-abdominal mass causing obstruction of the intestine or of the ureters or of both. One patient died because the large intra-abdominal mass of MF had obstructed the urinary tract and small bowel and had caused cardiorespiratory distress. In 11 patients small intestinal obstruction had occurred at least once, and in 10 patients surgical relief of the obstruction was necessary. In 7 patients the obstruction was caused by dense adhesions. In 3 patients the obstruction was caused by a large mesenteric mass of MF pressing directly on the intestine. In 1 patient obstruction was caused by puckering and distortion of the intestinal wall. In 7 patients the obstruction was relieved by lysis of the adhesions. In another patient obstruction was relieved by resection of the affected segment of bowel and partial resection of the mass of MF. In the tenth patient a gastrojejunostomy was necessary to circumvent the obstruction caused by a large unresectable mass of MF.

In 5 patients, obstruction of the urinary tract was confirmed by excretory urography. One of those patients required a permanent nephrostomy. Two patients were treated by ureterolysis; the other 2 have had recurrent attacks of pyelitis.

Intraoperative findings

MF was confined to the small intestinal mesentery in 12 patients (50%); it was located in both the

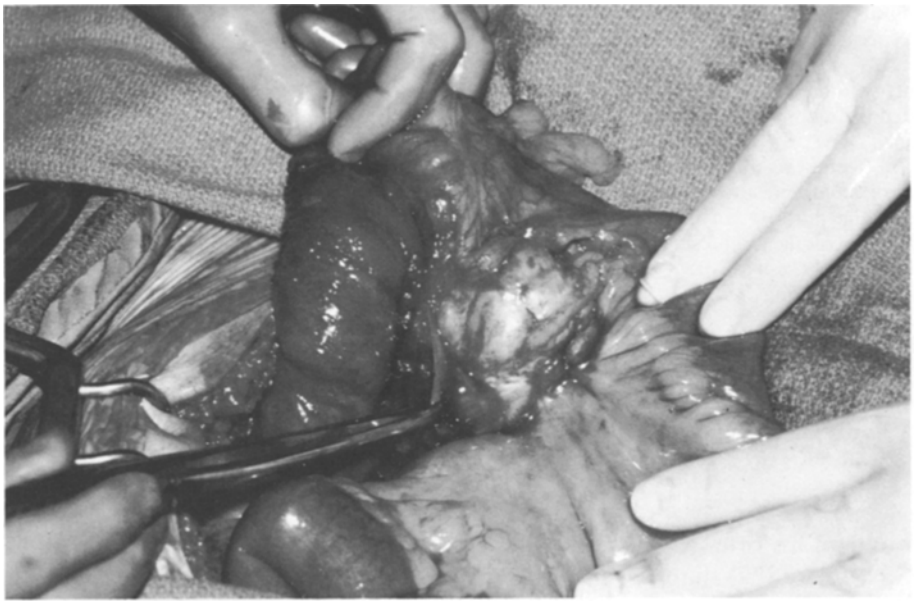

Fig. 1. Localized solitary mass in mesentery of ileum adjacent to ileocecal junction found at time of colectomy for familial adenomatous polyposis in patient who had had previous appendectomy

mesentery and the retroperitoneal area in 9 patients, in only the retroperitoneum in 1 patient, and in the transverse mesocolon in 1 patient.

In 18 of the 23 operated patients (78%) the MF was discrete and localized (Fig. 1). In the other 5 patients, either multiple flat white plaques were found in the small bowel mesentery or the root of the mesentery was diffusely involved with consequent retraction of the mesentery. In 14 patients (61%), the lesions were regarded as nonresectable either because of their location (engulfing the ureter or mesenteric vessels or both) or for fear of interfering with the blood supply to most of the intestine.

Surgical treatment

At the time of laparotomy, the surgeon considered the MF process to be resectable in 8 patients and unresectable in 13 patients. *Of the 8 patients with resectable lesions,* 5 underwent complete removal of the lesion. Three lesions recurred, and in 1 patient a short-bowel syndrome developed. The interval between resection of MF and diagnosis of its recurrence ranged between 2 and 4 years, and all recurrent lesions were deemed to be unresectable. One patient remains free of recurrence and symptoms 4 years after surgical treatment.

In 1 patient with a resectable lesion and in whom only a biopsy was done, small bowel obstruction due to dense adhesions occurred 4 years later. At operation, the size of the MF process was unchanged.

The other 2 resectable lesions, for which neither biopsy nor resection was done, have not caused any complications and have not enlarged clinically 4 and 5 years later.

Of the 13 patients with unresectable lesions, 6 patients underwent "debulking," and 5 of those patients have had further complications. In 4 of the 5 patients, complications could be directly attributed to further growth of the MF process. In the other patient the development of adhesions had caused small bowel obstruction. The sixth patient who had incomplete resection of the lesion was treated postoperatively with external beam radiation. She has been asymptomatic without recurrence or further growth of the MF for 12 years.

Biopsy alone was done in 6 patients, and 5 of these have not had any complications or obvious clinical growth of the MF. A sixth patient has required surgical exploration for adhesive small bowel obstruction, at which time the size of the original mass was unchanged.

The last of the 13 patients with unresectable MF that was neither biopsied nor resected has remained symptom-free for 8 years.

Postoperative complications

"Short-bowel syndrome" developed in one patient in whom extensive gangrene of the small intestine followed the radical resection of a large mass of MF. This syndrome also developed in another patient after repeated resections to relieve recurrent obstructions of the small intestine. In both patients,

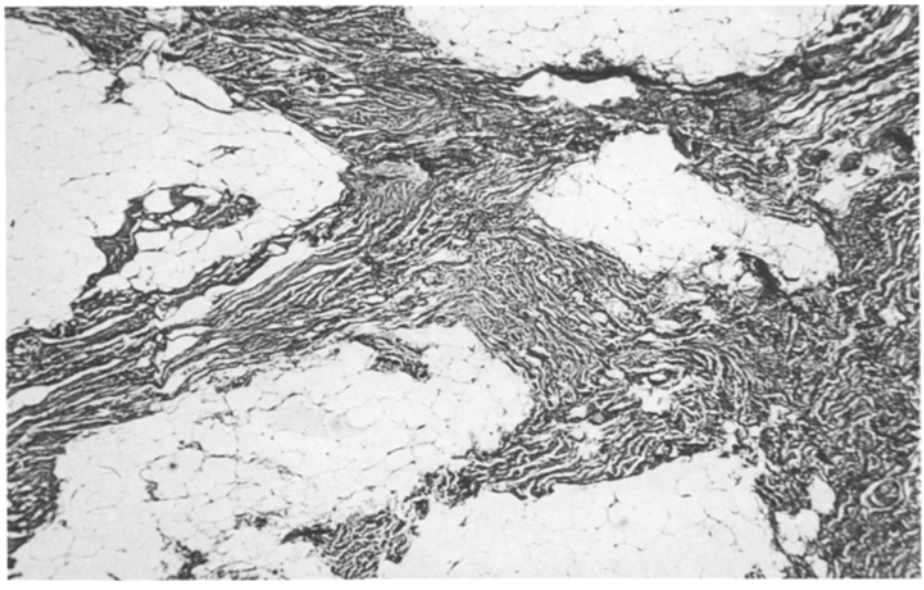

Fig. 2. Mesenteric fibromatosis. The process consists of an irregular proliferation of unencapsulated fibrous tissue that intermingles with the mesenteric adipose tissue. (Hematoxylin and eosin; ×120)

severe nutritional deficiency developed, and both required long-term parenteral nutrition.

An enteric fistula and intra-abdominal abscess developed in a patient after partial excision of the mass of MF together with a segment of the adjacent bowel. In another patient, that complication developed spontaneously as a result of the erosion of the bowel wall by MF. It is noteworthy that in 3 of the 4 patients in whom MF had developed spontaneously, complications occurred indicating that even without intra-abdominal surgery the disease can have an aggressive course and cause complications.

Nonsurgical treatment

Eight patients with either nonresectable recurrences or incompletely resected lesions were treated by various agents. Three patients were treated with sulindac (Clinoril), 100 mg twice daily, and tamoxifen (Nolvadex), 10 mg daily, in combination. In one of these patients, the mass is no longer clinically palpable, whereas in the other the mass was markedly reduced, as shown on computed tomographic scans of the abdomen. In the third patient, the mass has remained unchanged.

The other 5 patients have had no improvement of their condition with testolactone (1 patient), prednisone (2 patients), and indomethacin and ascorbic acid (2 patients).

Discussion

Nichols of the Mayo Clinic first described the association of MF with familial polyposis in 1923 [1], and later Smith further characterized the association [2]. This association was subsequently reported sporadically [3–6], but its hereditary significance was not appreciated until later [7]. Fibromatosis, including desmoid tumors, subcutaneous fibromatous lumps, and mesenteric lesions, are now regarded as one of the extracolonic "Gardner" manifestations of FAP [2, 5, 7–10]. Microscopically, the lesions are composed of proliferating fibroblasts mixed with variable amounts of the collagenous material produced by the fibroblasts (Fig. 2). The fibromatoses tend to be hypocellular lesions, and the presence of diffuse or focal hypercellularity sometimes suggests the possibility that the lesion might be a fibrosarcoma. Most fibromatoses have fairly prominent vascular spaces that often appear to be collapsed (Fig. 3), although this finding is not so common as in desmoid fibromatosis of somatic soft tissues.

Inflammation is not a component in fibromatosis unless there is associated ulceration of the adjacent viscus. In fact, the presence or more than a slight degree of inflammation should raise the possibility of mesenteric panniculitis (retractile mesenteritis) or idiopathic retroperitoneal fibrosis. The incidence, predisposing factors, and management of such lesions, including the exact role of surgery, have not been studied systematically.

The frequency of MF in patients with FAP is not known, but most authors have stated that the condition is more common in those patients with polyposis who have other extracolonic manifestations, especially soft tissue lesions [5]. Simpson [10] and Sener [9] reported a frequency of 2.7% and

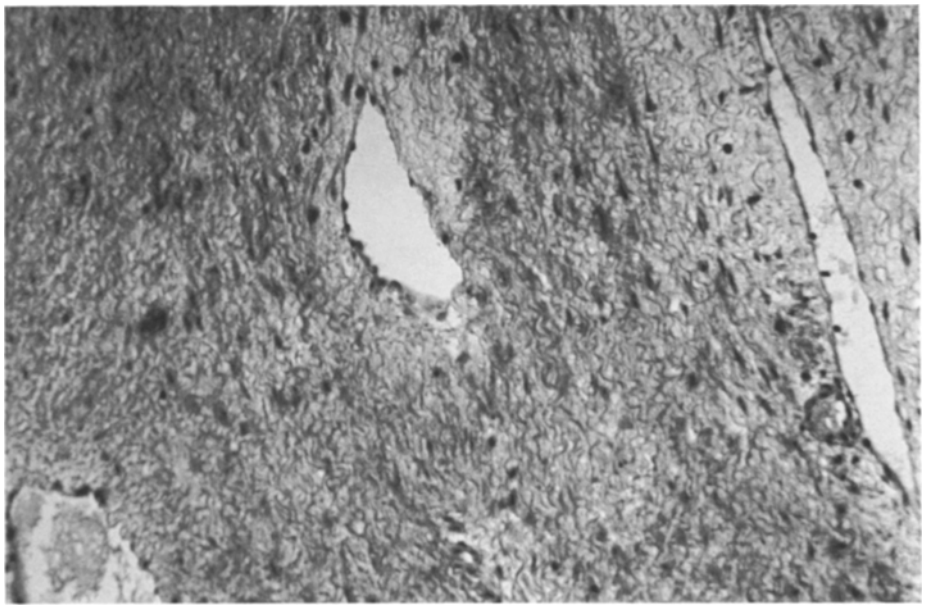

Fig. 3. Mesenteric fibromatosis. Higher magnification shows a hypocellular population and stellate and spindled fibroblasts. Dilated and slit-like vascular spaces are common and characteristic of fibromatosis. (Hematoxylin and eosin; ×480)

9%, respectively, in their studies of patients with FAP, whereas Naylor [11] reported 4 cases (14%) of mesenteric and retroperitoneal fibromatosis among the 28 affected persons in Gardner's original "Kindred 109." In none of these studies was the presence of extracolonic manifestations sought prospectively, and it was not until recently that MF was accepted as yet another extracolonic Gardner sign. In our retrospective analysis, the frequency with which this diagnosis was made was 13% in FAP patients and 28% in GS patients, or a total of 13% in the entire series of 183 patients. The apparent difference in frequency in the FAP and GS patients, however, may be spurious because, at least in the earlier years, not all of our patients with colonic polyposis were systematically examined for extracolonic signs. In particular, only a small minority have had endoscopic examinations of their upper gastrointestinal tracts. The higher incidence than previously reported may reflect the referral nature of our practice combined with an increased awareness of this condition in recent years. On the other hand, our observed frequency of 13% for MF may be an underestimate of the true frequency of MF because, not having attempted a systematic follow-up of all these patients, we cannot claim that we have identified all those in whom MF might have developed. Moreover, MF might develop later in those patients who do not have MF now. It will be recalled that in one of our patients, MF was not diagnosed until 28 years after the colectomy. The true frequency of MF in patients with colonic polyposis can only be determined by a prospective investigation through the patients' entire lifespans. Such an investigation would probably reveal that the true frequency of MF is much greater than our observed 13%. The important practical point, at the present time, is that we cannot predict in which FAP patients MF will develop. The presence of other Gardner signs (e.g., osteomas, sebaceous cysts, etc.) does not mean inevitably that MF will develop; the absence of those Gardner signs is certainly not a guarantee that MF will not develop.

The genetic mechanisms responsible for the Gardner lesions in patients with FAP are not known. Are the extracolonic lesions the pleiotropic effects of the same gene mutation that causes colonic polyposis, or are they produced by a second (somatic) mutation in the "polyposis gene," or is FAP with Gardner signs caused by a mutation in a gene that is not the same as the "polyposis gene"? We have seen three patients in whom MF was familial and others [7, 12–14] have made similar observations. Also, there seems to be a greater propensity for MF in women. The cause of MF is unknown. The majority of the reported cases of MF followed intra-abdominal surgery [2, 4, 15–18], although such lesions can certainly occur spontaneously [10, 12, 15, 19]. In our study, 85% of cases of MF seen were first noted after previous colectomy, and the majority of them were diagnosed within 4 years after operation. In 17% of our patients, however, MF appeared to have developed spontaneously.

In our own experience, debulking of nonresectable lesions was followed by regrowth in 5 of the 6 tumor masses. In contrast, if only a biopsy speci-

men was taken, as was done in 1 of the resectable and 6 of the nonresectable masses, no further growth was observed. Alternatively, recurrences of MF may be due to continued growth of the fibromatous process that is enhanced by surgical manipulations or trauma. What regulates the rate of growth of these lesions is unknown, but some observations suggest that hormones, especially estrogen, may play a regulatory role. These include the apparently higher incidence of MF in women during their reproductive years [18, 20–23], the apparent tendency of these tumors to develop during pregnancy or soon after [7, 24], the occasional observed regression of desmoid tumors after the menopause [23, 25–27], the production of similar lesions in laboratory animals by the administration of estrogen [14, 26, 28, 29], and the possible beneficial value of antiestrogen drugs [30–32].

Because surgical trauma may favor the development of MF, it becomes apparent that operative treatment should be reserved for lesions causing major complications and that it should be minimized as much as possible. Excision without sacrifice of intestine is desirable but is obviously difficult, if not impossible, to achieve unless the mesenteric lesions are small, do not involve major portions of the mesenteric blood supply, or are not located at the root of the mesentery. Unfortunately, this is rarely the situation, as exemplified by our series, in which two-thirds of the patients had nonresectable lesions. It is of interest, also, that even complete resection of the lesions is not only often ineffective but may actually promote recurrence and catastrophic complications. Some authors have reported good results after complete resection (12, 33], but most have not [17, 18, 34]. We believe aggressive resection of such mesenteric tumors, even for the relief of intestinal obstruction, is rarely indicated; our preference is for bypass followed by a trial of medical therapy. Small bowel obstruction occurred in nearly half of our MF patients, and in 70% of them, dense fibrotic adhesions were responsible.

Because many patients with FAP will now be explored with the hope of constructing an ileoanal anastomosis, the question arises as to the advisability of doing such a complex, complication-prone procedure should MF be unexpectedly encountered at laparotomy. If only small plaque-like lesions are encountered, especially if they are not located in the region of the terminal ileum, we have successfully constructed an ileoanal anastomosis without later complications. However, if a mass-like lesion is found, especially in the distal ileum, we prefer to proceed with ileorectostomy or Brooke ileostomy, depending on the extent of rectal polyposis.

Until recently, many drugs have been used in the management of MF and desmoid tumors with little or no success. Since the favorable report by Waddell et al. [32], the aggressive use of combination therapy has produced encouraging results [15, 34]. These have included estrogen antagonists, such as tamoxifen and testolactone [32], and nonsteroidal anti-inflammatory drugs, such as indomethacin and sulindac. We have observed good results with the combination of tamoxifen and sulindac in 2 of 3 patients reported here and in an additional 5 patients evaluated prospectively by computed tomographic scanning. These findings need further evaluation and longer follow-up, but they are certainly encouraging in such desperate situations.

The use of irradiation is debatable, but certainly in some cases a favorable response has ensued, perhaps because the radiation effect on the ovaries produces an artificial menopause. It is difficult, however, to confine radiotherapy to specified areas without damaging adjacent tissues, especially small bowel. Such damage may have disastrous consequences for the patient. Finally, one should keep in mind that occasionally MF may regress spontaneously.

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Accepted: 19 September 1988

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