Mesenteric desmoid tumours in Gardner's syndrome — review of medical treatments

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Summary: Gardner's syndrome comprises a triad of polyposis coli, osteomata and soft tissue tumours including desmoid tumours which can often present difficult problems in management. We report a patient with Gardner's syndrome treated with tamoxifen and medroxyprogesterone acetate. The literature on this rare syndrome and its management is reviewed.

Introduction

Gardner's syndrome (GS) comprises a triad of polyposis coli, osteomata and soft tissue tumours, with an autosomal dominant inheritance. Desmoid fibromatoses account for 45% of the soft tissue tumours¹ and occur in 3.5 to 29%² of patients with GS. Desmoid tumours are benign but locally invasive recurring neoplasms, consisting of mature fibroblasts within an extensive collagen matrix. Between 55 and 72% of these desmoid tumours are located within the mesentery.^{3,4}

There are at least 74 previously reported cases of mesenteric desmoid tumours associated with GS^{2,5–15} excluding double citations. In patients with GS, they usually develop after surgical procedures, such as pancolectomy.¹⁶ The extensive proliferative nature of the mesenteric tumour may lead to ureteric or intestinal obstruction or small bowel infarction. The tumours are difficult to treat, as they usually recur following resection. Several forms of drug treatment have therefore been tried. In this article, we report our experience of drug treatment in one patient and review previously reported experience in medical treatment of mesenteric desmoid tumours in Gardner's syndrome.

Case report

In August 1983, a 29 year old white female presented with an 18-month history of intermittent diarrhoea containing blood and mucus. Polyposis was diagnosed on endoscopy and she was treated with pancolectomy

and ileorectal anastomosis. In March 1985 she developed amenorrhoea, galactorrhoea and abdominal distension at which time she stopped taking a combined oral contraceptive. In May 1985, she again presented with lower abdominal colic and a dull pain in both flanks relieved by the frequent passage of normal stool. A palpable mass in the right iliac fossa was confirmed by ultrasonography and on computed tomography. Upper and lower gastrointestinal endoscopy revealed adenomatous polyps in the stomach and at the ileorectal anastomosis.

Laparotomy in May 1985 revealed a firm, white mass attached to the anterior abdominal wall and to the small bowel mesentery. A retroperitoneal tumour extended from the fourth part of the duodenum to the pelvic brim, and surrounded the superior mesenteric vessels. The tumour was not resectable. Biopsy revealed a desmoid tumour, remarkable only for the presence of eosinophils within the collagen matrix. Post-operative examination revealed a firm, fixed pelvic mass the size of a 20 week pregnancy; a pedunculated cutaneous polyp on the occiput (5 × 7 mm); an elevated soft tissue mass above the left mastoid process (3 × 5 mm) and over the spine extending from T10 to L1 (8 × 3 cm). Many new small (2 to 4 mm) maculopapular lesions were noted on the upper limbs, trunk and neck; the patient stated that these started as vesicular lesions which became pigmented and encrusted. Plain radiography showed an osteoma on the occiput (Figure 1) and in the mandible. A computed tomographic (CT) scan of the abdomen confirmed the surgical findings, and has been used to monitor treatment. CT scan of the head revealed no abnormality of the brain.

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Accepted: 10 February 1989.

Figure 1 Lateral radiograph of skull showing osteoma on occiput.

Relevant past history included an appendicectomy in July 1976 and two successful pregnancies. The patient had taken a combined oral contraceptive containing 50 µg of ethinyl oestradiol from June to December 1975, and another preparation containing 35 µg ethinyl oestradiol from October 1983 to March 1985. She had no family history of polyposis coli, although her mother died at age 49 from a malignant brain tumour of unknown histology. The patient's 10 year old daughter has had rectal polyps removed; her 8 year old son has frequent loose stools and is currently under investigation.

On recovery from laparotomy, the patient was started on a low-residue diet and her symptoms improved. She subsequently abandoned this diet without relapse. A trial of indomethacin was rapidly abandoned because the patient developed abdominal pain. Tamoxifen 20 mg daily was started in June 1985 at which time the patient had no symptoms. Physical examination in September 1985 showed no change in the size of the pelvic or soft tissue masses, and an abdominal CT scan revealed no change in the former. In February 1986, the patient developed further abdominal colic and an abdominal CT scan showed enlargement of the mass in two of the three dimensions. The soft tissue masses were no longer palpable. Tamoxifen was stopped and medroxyprogesterone 100 mg thrice daily was started. The colic resolved and the abdominal mass remained unchanged on clinical examination and CT scan (Figure 2) until September 1986. The patient then developed further colic followed by intestinal obstruction, and eventually underwent resection of a 2.9 kg desmoid tumour surrounding the mesenteric vessels together with much of the

Figure 2 CT scan of abdomen showing enormous anterior desmoid tumour, shortly before resection.

small bowel and rectum which were involved with the tumour. She was left with 60 cm of proximal small bowel and a terminal jejunostomy. It proved impossible to maintain nutrition and fluid balance by oral feeding, and home total parenteral nutrition was instituted. The patient remains well on this programme to date, and is also eating a little as desired.

Discussion

The reported occurrence of familial polyposis coli (FPC) and Gardner's syndrome (GS) within the same family suggests a single pleiotropic gene with variable expressivity.^{1,17} Of 34 patients with FPC in one study 35% had a single extraintestinal manifestation of GS and an additional 38% had the full triad on further investigation.¹⁸ In a group of 29 patients with FPC and desmoid tumours, 26 of which were mesenteric, 19 had extracolonic manifestations.¹⁹ A review of 459 patients with FPC by Utsunomiya²⁰ found that 36% showed single extracolonic trait and 7% displayed the characteristic triad. Several authors have suggested that there are no clinically significant differences between GS and FPC.^{4,21}

Mesenteric tumours in GS usually follow abdominal surgery such as prophylactic abdominal colectomy for polyposis coli,^{1,2,22} after an average 2.5 years.¹⁰ Three cases of spontaneous occurrence discovered at initial surgery have been reported.^{2,23} Mesenteric and abdominal wall desmoid formation appears to be induced by surgical trauma and there is up to a 50% recurrence rate despite wide resection. Harvey,⁹ Naylor²³ and Nance¹⁶ recommend that resection of mesenteric desmoid tumours be avoided regardless of tumour size due to stimulation of tumour growth and involvement of major local structures. Jones¹⁹ and Steger¹⁵ state that because of surgical

complexity of adequate excision of mesenteric desmoids and frequency of recurrences, surgery should be reserved for relief of symptomatic obstructions. Occasional successful resection without recurrence has been reported,^{1-3,24} and one recent editorial considered surgery the only appropriate treatment.²⁵

Desmoid tumours have a 4% overall spontaneous regression rate.²⁶ There have been five reported cases of spontaneous remission of desmoid tumours^{26,27} but only one of these was associated with GS or FPC.¹⁹

It is difficult to assess the efficacy of different drug treatments for mesenteric desmoid tumours because of differences in clinical assessment, in therapeutic combinations and in the quantitation of response, and because of the small numbers involved in each report. The treatments that have been reported to cause at least partial regression of mesenteric desmoid tumours in GS and the experiences with each drug are summarized in Table I.

The rationale for endocrine therapy of desmoid tumours is based on the probable hormonal influence upon their growth. In Gardner's syndrome, desmoid tumours seem to have developed after pregnancy^{1,9,22} and following exposure to oral contraceptives.^{29,30}

Oestrogens appear to stimulate growth,^{28,30} and in particular a predominance of oestrogen over progesterone.²⁶ Oestrogens have produced fibrous tumours in rats whilst progesterone inhibited their development.³¹ In desmoid tumours not specifically associated with FPC, progestogens produced a 72% partial response rate (8 of 11 patients).³⁰ Oestrogen receptors have been found in the cytosol fraction of desmoid tumours from premenopausal women,²⁶ and in three of four desmoid tumours, Reitamo demonstrated the presence of oestradiol receptors whilst progesterone receptors were absent.³²

Irradiation of abdominal desmoid tumours has proved successful occasionally,^{1,14} but perhaps only by inducing menopause since only women receiving total abdominal radiation respond, and male patients do not respond.^{22,28} In patients with extra-abdominal desmoid tumours unassociated with GS, however, prolonged megavoltage irradiation (greater than 50 gray for up to two years) has produced a 59% complete and 18% partial response rate in a series of 17 patients.³⁴

Our patient has gastric and rectal polyps following pancolectomy. Extracolonic polyps can be found in

Table I Treatment of mesenteric desmoid tumours in Gardner's syndrome

	Number of patients responding			Reference
	CR	PR	NR	
Testololactone		2	3	1, 9, 14, 24
NSAID	1 [1]	1 [5]	[5]	4, 14 19, 35, 51
Tamoxifen	1			29
Tamoxifen + cytotoxic agent			1	22
Tamoxifen + NSAID	1	1 [2]	1 [1]	14, 52 19, 35
Cytotoxic drugs	2 [1]	[2]	1 [5]	1, 22, 24 19, 24
Radiotherapy	[1]	[1]	1 [3]	2 19, 34, 52
Surgery	4 [4]	1	5 [3]	2, 9, 24 24, 26
Progesterone	[6]	[3]	[3]	30, 35
NSAID + ascorbic acid + cytotoxic agent			[1]	14
Surgery + testololactone			[1]	24
Spontaneous	[5]			19, 26, 27

N.B.: NSAID = Non-steroidal anti-inflammatory drug; CR = complete regression; PR = partial regression; NR = no regression; [] = response by non-Gardner's syndrome patients

82% of patients with FPC.³⁶ Gastric polyps occur in approximately 70% of patients with FPC or GS³⁷⁻⁴¹ while duodenal polyps occur in 60 to 100% of patients.³² Adenomatous polyps of the gastric fundus occur in 24% of patients with GS,⁴³ are relatively specific for FPC/GS,²³ and do not demonstrate a propensity for malignant transformation.^{43,44} The mean age of patients with FPC having gastric polyps is 36.6 years, compared with an incidence of only 1.8% in the general population between the ages of 30 to 40 years old.³⁷ Gastric polyps in FPC tend to occur later in life and have a slower growth compared to colonic polyps in these patients.³⁷ Duodenal polyps occur in about 50% of patients with GS^{40,43} and in about 90% of patients with FPC.³⁸ These are more likely to precede development of duodenal or periampullary carcinoma. There was only one case of gastric carcinoma in a report of 144 patients with FPC.¹⁷ There are only two cases in the GS literature^{8,45} and eleven reported cases in the FPC literature^{8,17,46} of gastric carcinoma. Eight of the FPC gastric malignancies were reported from Japan. The occurrence of stomach cancer among patients with FPC in Japan is 2.6%, which is lower than that expected in the Japanese population.⁴⁷

Periampullary carcinoma represented the second most frequently diagnosed malignancy in patients with FPC/GS, following colon carcinoma. Periampullary carcinoma has been estimated to occur in 2 to 3% of patients with FPC, compared with a frequency of 0.02 to 0.05% in the general population, representing a 100- to 200-fold increased risk.⁴⁸ The average age at diagnosis of periampullary carcinoma was 46 years old, a decade earlier than the average age in the general population.^{42,48} Periampullary carcinoma is usually

diagnosed 15.7 years following diagnosis of colonic polyposis.⁴²

Colon carcinoma develops in virtually all patients with FPC/GS, usually by the age of 35 to 40.^{49,50} Pancolectomy with ileorectal anastomosis does not seem to remove the risk of rectal carcinoma. Moertal⁵⁰ found a 100-fold increase above the age specific rate in the incidence of rectal carcinoma in patients who had undergone colectomy with ileorectal anastomosis followed by periodic removal of rectal polyps; the prevalence ranged from 5% at 5-year follow-up to 59% at 23 years among 178 patients. He suggested that rectal cancer might arise in patients with polyposis *de novo* without malignant transformation of existent rectal polyps. Fulguration of rectal polyps would therefore not decrease the risk of rectal carcinoma. Harvey,⁹ however, recommended conservative local removal of rectal polyps.

No case of malignant desmoid tumour has been reported²⁸ after careful histopathological differentiation from fibrosarcoma.² One patient had developed a fibrosarcoma within a mesenteric desmoid tumour 7 years after extensive irradiation.²²

In summary, mesenteric desmoid tumours are a common, and sometimes troublesome feature of Gardner's syndrome. They usually follow abdominal surgery such as colectomy for concomitant polyposis, and further surgery is seldom curative. Oestrogen containing oral contraceptives and pregnancy may stimulate tumour growth in women, and laparoscopic sterilization is probably best avoided lest it induce further tumour growth. The anti-oestrogen tamoxifen and progestogens may inhibit tumour proliferation, and surgical intervention should be reserved for relief of inevitable intestinal or ureteral obstructions.

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