Treatment of Desmoid Tumors in Gardner's Syndrome

Report of a Case

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Itoh H, Ikeda S, Oohata Y, Iida M, Inoue T, Onitsuka H. Treatment of desmoid tumors in Gardiner's syndrome: report of a case. Dis Colon Rectum 1988;31:459–461.

Aggressive desmoid tumors present difficult problems among patients with Gardner's syndrome. Recently, attention has been directed toward metabolic or hormonal manipulation of these tumors. A 21-year-old woman with Gardner's syndrome was admitted because of recurrent abdominal wall tumors. She was treated with nonsteroidal anti-inflammatory drugs, tamoxifen, and ascorbate for seven months. During this therapy, CT scan showed a gradual increase in size of the tumors. Subsequent resection of the abdominal tumors and the colon was performed. Although these three types of drugs were administered to prevent postoperative recurrence, an abdominal wall desmoid tumor that invaded the mesentery developed within nine months. The known treatments, that is, chemotherapy, irradiation, and surgical resection are discussed in view of this experience. [Key words: Desmoid tumor; Fibromatosis; Gardner's syndrome; Anti-inflammatory drugs]

DESMOID TUMORS IN the abdominal wall or abdominal cavity are often inoperable, amenable to only partial excision or removal with great risk of complications and mortality. Although the histologic characteristics are benign, local recurrence is common.[1–3] Waddell *et al.*[4–6] and Belliveau and Graham[7] postulated that nonsteroidal anti-inflammatory drugs, tamoxifen, and ascorbate might be effective for tumor regression. These drugs were administered to this patient with desmoid tumors associated with Gardner's syndrome before and after surgery. Various treatments are discussed with the literature reviewed.

Received for publication April 8, 1987.

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Report of a Case

A 21-year-old Japanese woman with huge abdominal lumps and pain was admitted to Kyushu University Hospital in April 1984. She noted that multiple, soft, subcutaneous tumors had been present since early childhood. A retroperitoneal tumor, diagnosed histologically as neurofibroma, was resected when she was 15 years old. In August 1981, she underwent cholecystectomy and extirpation of abdominal wall tumors that were diagnosed histologically as fibromatosis. Six months later, the abdominal wall tumors had recurred and increased in size. Her mother died of rectal cancer associated with Gardner's syndrome at the age of 34.

On admission, the abdominal tumors measured approximately 10 × 15 × 10, 9 × 7 × 7, and 8 × 5 × 5 cm. Multiple subcutaneous tumors, one of which was an epidermal cyst, were seen in the neck, back, hip, and extremities. A panoramic x-ray of the mandible revealed two osteomas, an odontoma, and impacted teeth. Barium meal study and fiberscopic examinations (including biopsies) revealed fundic-gland polyposis of the stomach and duodenal adenomas. Barium-enema and fiberoptic examinations showed multiple adenomas in the large bowel. CT scanning showed huge abdominopelvic masses.

On April 23, 1984, she was put on sulindac, 400 mg, tamoxifen, 30 mg, and ascorbate, 1500 mg, per day. In June she complained of epigastralgia and nausea and was diagnosed endoscopically as having a gastric ulcer. Since July 1984, indomethacin suppositories were prescribed instead of sulindac. During this chemotherapy, the abdominal masses gradually increased in size. On October 30, tegafur, 600 mg, and uracil, 1334 mg per day, were prescribed instead of the indomethacin suppository, but the abdominal masses continued to enlarge.

Because of pain and edema of the left leg, she underwent extirpation of the abdominal wall masses, which consisted of three parts, and total colectomy with ileorectal anastomosis on December 7, 1984. One of the desmoid tumors involved part of the jejunum, which was resected, and an end-to-end anastomosis was done. The defect in the abdominal wall was closed primarily. The abdominal wall tumors weighed 5400 gm,

TABLE 1. *Effects of Chemical Treatment on Desmoid Tumors*

Reference	Administered Drugs	Frequency of Regression (Complete Regression)
Waddell *et al.*[6]	Indomethacin Sulindac Tamoxifen Ascorbate	6/7 (2/7)
Belliveau and Graham[7]	Sulindac	1/1 (0/1)
Khorsand and Karakousis[16]	Doxorubicine Actinomycin D Vincristine	1/1 (1/1)
Kinzbrunner *et al.*[26]	Tamoxifen	1/1 (0/1)
Arellano Perez *et al.*[27]	Antiestrogens	1/1 (0/1)
Lanari[28]	Progesterone Medroxyprogesterone	7/10 (7/10)
Panos and Poth[29]	Prednisone	1/1 (1/1)
TOTAL		18/22 (11/22)

TABLE 2. *Effect of Radiotherapy on Desmoid Tumors*

Reference	Site of Tumor	Frequency of Regression (Complete Regression)
Pack and Ariel[9]	Abdominal Wall	5/6 (2/6)
Rock *et al.*[23]	Extra-abdominal	25/81 (5/81)
Greenberg *et al.*[34]	Extra-abdominal	5/6 (1/6)
	Abdominal wall	1/1 (90% reduction)
	Mesentery	1/1 (1/1)
Jones *et al.*[2]	Intra-abdominal	0/2 (0/2)
Kiel and Suit[35]	Extra-abdominal	7/8 (4/8)
	Abdominal wall	1/1 (1/1)
	Mesentery	1/1 (0/1)
Leibel *et al.*[36]	Extra-abdominal	16/16 (11/16)
	Pelvis	1/1 (1/1)
	Abdominal wall	1/1 (1/1)
	Mesentery	0/1 (0/1)
Cole and Guiss[37]	Extra-abominal	1/3 (1/3)
Assad *et al.*[38]	Extra-abdominal	6/8 (6/8)
	Abdominal wall	1/1 (1/1)
	Pelvis	1/1 (1/1)
TOTAL		73/139 (36/139)

2900 gm, and 400 gm, respectively. Histologic examination of the tumors and large bowel revealed fibromatosis and adenomatosis of the colon. The postoperative course was uneventful and she was discharged without abdominal wall hernia. Postoperatively, sulindac, 400 mg, tamoxifen, 30 mg, and ascorbic acid, 750 mg, were administered daily to prevent recurrence of the desmoid tumors. In spite of this adjuvant chemotherapy, an abdominal mass developed within eight months and gradually increased. The mass has invaded the mesentery to the extent that it could not be removed. If severe symptoms appear, radiotherapy will be the treatment of choice.

Discussion

The term desmoid, first introduced by Johannes Mueller in 1838, is based on the tendon or bandlike appearance of the tumors.[8-10] Classically, desmoid tumors were considered to be tumors of the anterior abdominal wall, which develop as a result of trauma, but it is now recognized that they can appear in musculoaponeurotic structures throughout the body. Desmoid tumors are composed of mature fibroblasts, and have no true capsule. They compress and infiltrate surrounding tissue.[1-3,8-10]

The incidence of desmoid tumors, based on the case records of the Finland Hospitals, was 2.4 ± 1.1 in 10^6 inhabitants per year,[11] and the incidence in Gardner's syndrome patients has been reported to be from 3.5 to 17.5 percent.[2,10,12,13] In spite of their benign histologic appearance, successful management of desmoids has been difficult because of the potential to attain a large size, the tendency to aggressive infiltration of adjacent tissue, and the risk of recurrence. The recurrence rate is estimated to be 25 to 65 percent.[1,2,10,14-19] Concerning the extent of surgical resection, it has been reported that the incidence of local recurrence can be as high as 65 percent with simple excision and 40 percent with wide extirpation.[16,17]

Several cases with spontaneous or postmenopausal regression of the tumors have been reported.[1,18-22] Rock *et al.*[23] reported that in 60 of 68 patients with desmoid tumors, the tumor activity decreased after an average follow-up of 6.3 years. But, when uncontrolled, these tumors may lead to severe local morbidity, even death.[2,3,14,23-25] Treatment of desmoid tumors with nonsteroidal anti-inflammatory compounds, estrogen blockades, and/or ascorbate is summarized in Table 1.

Waddell *et al.*[4-6] found that administration of indomethacin caused complete resolution of desmoid tumors after a partial response to radiation. The predominant action of indomethacin is inhibition of prostaglandin synthesis and, consequently, might promote immunologic attack on tumor cells. Furthermore, indomethacin and ascorbic acid lower cyclic adenosine monophosphate in tumor cells, with an interruption of the cell cycle and inhibit ornithine decarboxylase, an enzyme associated with tumor proliferation.[4-6]

Approximately 80 percent of these tumors occur in women, especially during the fertile years.[3,11] Reitamo *et al.*[11] stated that fertile female patients with desmoid tumors had a significant predisposition to estrogen dominance and deviation from progesterone dominance. The estrogen receptor was present in 33 percent of desmoid tumors assayed (5/15) and the density was significantly higher than in healthy control tissue.[11,30] The effect of estrogen blockade seems to be a restriction of RNA synthesis and alteration in transcription of genes involved in

tumor growth.[6,7,26] Tamoxifen is reported to inhibit prostaglandin synthesis and to be effective in the treatment of desmoid tumors.[1,6,7,26] Andrada *et al.*[31] reported that the fibroblast cells were destroyed by the progesterone and not by a bioproduct of its metabolism.

Radiation or adjuvant radiotherapy has achieved partial or complete regression[23,32-38] as seen in Table 2. However, several reports stated that desmoid tumors were insensitive to irradiation.[1,2,19,20,39] Some have suggested that these effects were due to an indirect effect of radiation on ovarian function.[3,9,26] Rock *et al.*[23] noted that out of 81 patients who received radiotherapy, 5 were cured, 20 had no further increase in the size of the tumor, and tumor growth was not controlled in the remaining patients.

In this study's patient, nonsteroidal anti-inflammatory drugs, ascorbic acid, and tamoxifen were prescribed in attempts to control the large desmoid tumors, preoperatively and as postoperative adjuvant chemotherapy. However, these drugs did not decrease the size of the tumor or prevent a recurrence in this case. Thus, aggressive radical surgery and/or radiotherapy is now under consideration. It has not been established which therapy would be the first choice or how long it should be continued. The authors must wait for more detailed cytochemical studies and controlled multicenter trials for better treatment of desmoid tumors.

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