Endocrine Therapy for Desmoid Tumors

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Two female patients with desmoid tumors (aggressive fibromatosis) showed tumor regression after endocrine therapy. In one patient, tumor response to tamoxifen has been maintained over several years of treatment. In the second patient, who had inoperable mesenteric fibromatosis, the tumor progressed on tamoxifen but regressed after treatment with Zoladex (goserelin acetate, ICI, Melbourne, Australia) and medroxyprogesterone acetate (MPA). To the authors' knowledge this is the first report of the use of Zoladex in the treatment of desmoid tumors. This review of the literature reveals that the biology of this disease is related to the endogenous hormonal environment and that estrogen receptors have been documented in desmoid tumors. Thirty-five cases are identified where endocrine agents have been employed, with a response rate of 51%. Furthermore, tumors may respond to second-line hormonal therapy after failing to respond to initial endocrine treatment. Endocrine treatments have also been used in other disorders of fibroblastic origin. The authors recommend that endocrine treatment be employed in inoperable desmoid tumors or where there has been postsurgical recurrence. In addition, the role for endocrine therapy in other soft tissue neoplasms should be determined. Cancer 68:1384-1388, 1991.

AGGRESSIVE FIBROMATOSES, or desmoid tumors, are benign neoplasms mainly arising from fascial sheaths and musculoaponeurotic structures. They are locally invasive but do not metastasize. Histologically they are characterized by fibroblastic cells with elongated nuclei which appear almost normal. There is often a whorled appearance, reminiscent of a uterine fibroid. Mitotic figures are uncommon.1,2

They are rare tumors, only 17 being described among over 50,000 first hospital admissions for neoplastic disease in one early series.3 Reitamo et al.2 suggest an incidence of 3.7 ± 1.3 new cases per 106 of the population per year. The tumor arises in the abdominal region in about 50% of the cases2 and extraabdominal disease occurs most frequently in the shoulder girdle, inguinal region, and lower extremities.1,4,5 Desmoid tumors are more common in women, particularly in those of child-bearing age6 but the precise sex ratio varies considerably from series to series. Although there is no direct association with uterine fibroids, the histologic features and sex distribution suggest the possibility of common features. Trauma, surgical or otherwise, is thought to be an etiologic factor in the development of some desmoids.

The association between desmoid tumors and familial adenomatous polyposis (FAP) was first noticed in 1923 by Nichols of the Mayo Clinic,7 and subsequent authors have described an even closer association with the FAP subgroup, Gardner's syndrome. Lotfi et al.8 report an incidence of 13% in FAP patients and 38% in patients with Gardner's syndrome. However, of patients with aggressive fibromatosis few have colonic polyposis. Reitamo et al.2 investigated 75 patients with aggressive fibromatosis and found only one case of Gardner’s syndrome. They did find, though, an 80% incidence of the musculoskeletal abnormalities associated with Gardner’s syndrome (such as cortical thinning and exostosis) among aggressive fibromatosis patients, and suggested a common genetic predisposition.

The standard treatment of aggressive fibromatosis has been surgical excision. Several authors have emphasized the need for wide excision because of the risk of local recurrence.3,5,9,10 Khorsand and Karakousis4 report a local recurrence rate of 25% to 40%, whereas in other series recurrence rates have varied from as low as 10% to as high...
as 90%. In an overview of ten surgical series, Keil and Suit found a mean incidence of local recurrence of 45%.

Radiation therapy has also been advocated either in primary management or as an adjunct to surgery. Again, a wide variety of success rates has been published. Keil and Suit point out that early series with low rates of tumor control used low doses of radiation. In their series of 25 patients local control was achieved in 76% of cases, with consistent complete control when radiation doses above 6000 cGy were used. Wara et al. reported local control in 81% of 16 cases with a mean tumor dose of 5000 cGy delivered in 180-cGy fractions. Pack and Ehrlich suggested that some of the results attributed to radiation therapy in women may be due to radiation-induced ovarian failure. It is notable that the pelvic desmoids in this series all achieved complete remissions, although the sex of the patients is not stated.

Over the last 20 years, endocrine aspects of desmoid tumors have attracted attention. The preponderance of cases in women of child-bearing age and reports of spontaneous tumor regression during menarche and menopause raised the possibility of endocrine therapies. Case reports over the last decade have documented response to antiestrogens and progesterational agents, although other authors have reported a lack of response with the same agents.

We report two patients with aggressive fibromatosis who were treated with endocrine agents, including, to our knowledge, the first use of the luteinizing hormone releasing hormone (LHRH) analogue Zoladex (goserelin acetate, ICI, Melbourne, Australia) in this condition.

Case Reports

Case 1

A 40-year-old woman was referred in 1982 for advice about recurrent tumors of the left lower leg. From early life she had noticed some asymmetry of the legs and at the age of 34 had developed a mass in the medial aspect of the left calf. This persisted and was excised some 5 years later. Histopathologic examination revealed an aggressive fibromatosis of desmoid type. One year later the mass recurred and a biopsy specimen again showed the histologic features of aggressive fibromatosis.

She was an otherwise well woman. There was no family history or past history of soft tissue tumors, colonic polyps, or colorectal cancer. She was premenopausal. Examination revealed three discrete soft tissue masses in the popliteal fossa and on the lateral aspect of the left calf, the largest measuring 5 × 5 cm. There were no other significant physical findings. She was prescribed tamoxifen (20 mg daily).

Over the subsequent years, the masses slowly reduced in size. After 2 years there was a single 2-cm mass evident. Eight years after tamoxifen was started, the only abnormality detectable is a small ill-defined nodule over the old surgical scar. Biopsy was not performed.

Case 2

A 40-year-old woman presented to her local doctor in February 1989 with a 12-month history of abdominal discomfort which had increased over the previous 5 weeks. An abdominal mass was noticed and she was referred to a surgeon. A fine needle aspiration biopsy revealed cells thought to be from a sarcoma, and after an aortogram, a laparotomy was performed. There was a locally invasive tumor completely occupying the small bowel mesentery, extending to the ileum and across toward the ascending colon. There was no evidence of metastasis. Biopsy was performed on the tumor, but it was considered unresectable unless total removal of the small bowel was performed. The histopathologic findings were of aggressive fibromatosis.

There was no family history of fibrous tumors or colonic polyps. Menstruation was normal and there had been two pregnancies but no children. Examination revealed a large left-sided abdominal mass which was firm but nontender. Computerized tomography (CT) scan (Fig. 1) demonstrated the tumor mass with no evidence of metastasis. The patient was prescribed tamoxifen (20 mg daily).

Two months later, there was both clinical and CT evidence of disease progression. Tamoxifen was ceased and the patient commenced treatment with the LHRH analogue, Zoladex. Zoladex suppresses secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and in this way reduces end organ production of androgens in men and of estrogen in women. It has been used in the management of prostate cancer and is currently being evaluated in the treatment of advanced breast cancer. It causes reduction in the size of uterine fibroids.

Three and a half months after the introduction of Zoladex, there was again CT and clinical evidence of an increasing abdominal mass without metastasis. Medroxyprogesterone acetate (MPA) 500 mg daily was added, and after this there was a slow reduction in size.

FIG. 1. CT scan of the abdomen showing huge mesenteric tumor.
but consistent reduction in tumor size documented on CT (Fig. 2). After 10 months of this therapy the patient is free of symptoms and the only clinical evidence of disease is an ill-defined mass in the left side of the abdomen. She has ceased menstruating and gained 9 kg in weight. Weight gain has caused distress and the dose of MPA has recently been reduced to 200 mg daily, but tumor shrinkage has continued.

Discussion

Although the precise relationship between desmoid tumors, the endogenous hormonal environment, and exogenously administered endocrine therapies is far from clear, it is a relationship which is now well established. It may lead to a change in the primary treatment of this uncommon tumor as well as have implications for the biology of fibrous tissue neoplasms in general. Patient 1 provides a straightforward if anecdotal example of tumor response to an antiestrogen, and is consistent with published reports.

Patient 2 raises new issues in the management of this disease, the first being the use of an LHRH analogue, not previously noticed in the published literature. Its role in producing a response in our case is not clear as response was achieved only after the addition of MPA to treatment. Secondly the fact that the tumor responded to MPA (plus Zoladex) after evidence of progression during tamoxifen therapy suggests that these agents may act through different pathways. Second-line therapy in these tumors has only rarely been reported. Balducci et al. described a patient whose tumor failed to respond to progesterone but regressed after treatment with tamoxifen.

Whereas the use of antiestrogens and progestational agents in the management of desmoid tumors remains anecdotal, there is mounting evidence that an endocrine approach is a rational one. Reference has already been made to the incidence of this tumor in women of childbearing age and the influence that both menopause and menarche may have on its behavior. Animal models have demonstrated the development of fibrous tumors upon prolonged exposure to estrogens and subsequent tumor regression after progesterone treatment. Svanrik et al. reported the development of an abdominal wall desmoid in a man treated with high-dose estradiol for prostate cancer.

In recent reviews of desmoid tumors, Reitamo et al. examined hormonal aspects of the disease from a biological standpoint. In a series of 89 patients they analyzed patient sex and age, tumor site, and tumor behavior. They reported that in the group younger than 15 years, desmoid tumors were predominantly extraabdominal and tended to occur in girls, whereas between the ages of 18 and 36 years, abdominal tumors were more than ten times more frequent than extraabdominal tumors, with a female preponderance of 1.8 to 1. In old age, abdominal and extraabdominal tumors were equally frequent and the sex incidence was equal. Tumor growth rates were faster in women than in men (two times so in fertile life, four times so at menopause) but after menopause it approached that of men. The hormonal environment, then, appears to have a profound effect on tumor behavior.

It is not surprising, therefore, that investigators have searched for physiologic correlates. Reitamo et al. detected estrogen receptors (ER) in two of four tumors examined. Lim et al. reported a series of 15 tumors (9 from women, 6 from men). They found a 33% incidence of ER positivity with equal sex distribution, and evidence of antiestrogen binding sites in 79% of cases. ER levels were higher in women although overall levels were low (4.93 to 44.67 fmol/mg protein). The significance of these findings is not clear.

The understanding of the biology and pathophysiology of aggressive fibromatosis is still at an early stage, and the rarity of the disease makes it difficult to develop clinical management guidelines. It is apparent that the results of both surgery and radiation therapy remain less than satisfactory in many if not most patients.

The true role of endocrine therapy remains unknown. Failure of endocrine therapy is less likely to be reported than success and it is difficult to imagine prospective randomized trials involving withholding such well tolerated but potentially therapeutic drugs. Specific questions of importance relate to treatment regimens: How many endocrine therapies should be tried, in what order, and whether singly or in combination? Our experience with Patient 2 suggests that failure of one endocrine therapy does not necessarily indicate resistance to other endocrine agents.
Reitamo et al. have demonstrated differences in tumor behavior in male and female patients, but it is not known whether the response rates to endocrine treatments are different. However, progesterone therapy has caused responses in men with desmoids. In addition, there may be differences in tumor biology between desmoids associated with FAP and those not.

Examination of the available data (Table 1) shows that 35 desmoid tumors treated with endocrine therapy were a response in 18 (51%). The response rate for desmoids associated with Gardner’s syndrome or familial adenomatous polyposis was 40% (6 of 15) whereas in de novo desmoids, the response rate was 60%. This difference does not reach statistical significance.

Of patients failing initial endocrine treatment (Table 2), only three patients (18%) were given second-line therapy, and two responded. Although it is therefore not possible to estimate the rate of response to second-line treatment, the overall response to endocrine treatment might be significantly higher than 50% if second-line drugs were routinely offered.

Endocrine effects in soft tissue dysplasia are not limited to desmoids. Uterine fibroids have been shown to respond to LHRH analogues and Lanari has treated conditions such as mediastinal fibrosis, retroperitoneal fibrosis, and lymphangiomyomatosis with MPA with good effect in both males and female patients. Palmar fibromatosis (Dupuytren’s contracture) is thought to be related to disordered estrogen metabolism in chronic liver disease. Mackenzie has argued that several conditions of fibroblastic origin, proliferative but nonmetastasizing, should be regarded as variations of a single clinicopathologic entity. The relationship between desmoids, uterine fibroids, and other fibromatosis on the one hand, and fibrosarcomas on the other is not clear, but it is possible that some sarcomas may be endocrine responsive.

In summary, a review of the literature suggests that desmoid tumors frequently respond to endocrine therapy, and that failure with one agent does not preclude success with another. Endocrine therapy is recommended in inoperable cases, but might also be employed in postsurgical recurrences and in the preoperative setting. Last, there may be implications for the biology of other soft tissue neoplasms.

REFERENCES

### Table 1. Use of Endocrine Therapy for Desmoid Tumors

<table>
<thead>
<tr>
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NSAID: nonsteroidal antiinflammatory drugs; MPA: medroxyprogesterone acetate.

* Associated with Gardner’s syndrome or familial adenomatous polyposis.

### Table 2. Endocrine Treatment Failures

<table>
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MPA: medroxyprogesterone acetate.


