ELSEVIER

REGRESSION OF LARGE PELVIC DESMOID TUMOR BY TAMOXIFEN AND SULINDAC

JOSEPH K. IZES,* LEONARD N. ZINMAN, AND CARL R. LARSEN

ABSTRACT

A 54-year-old man was evaluated for symptoms of bladder outlet obstruction. Evaluation revealed a 10 by 9.8-cm tumor composed of bland, fibroblastic, poorly cellular material adjacent to the prostate. Administration of a course of antiestrogen (tamoxifen) and a nonsteroidal anti-inflammatory agent (sulindac) resulted in prompt relief of symptoms and a slow decrease in the size of the tumor as measured by computed tomography. After 54 months of therapy, the tumor was undetectable clinically and dramatically reduced in size as seen on computed tomography. Data on the natural history of desmoid tumors and the efficacy of various therapeutic strategies are reviewed. UROLOGY® **47**: 756–759, 1996.

The optimal curative treatment of patients with desmoid tumors has yet to be defined. These locally invasive, slow growing, nonmetastasizing neoplasms, which are believed to arise from fascial tissues, may involve any region of the body. Primary therapy is usually considered to be complete surgical excision. However, even with total excision and adequate margins, a significant rate of recurrence, ranging from 19% to 77%, has been reported.[1,2] Conversely, the literature contains reports of spontaneous regression without therapy[3] and low rates of local recurrence even in the presence of positive margins.[4]

Retroperitoneal desmoid tumors are rare, occurring in less than 20% of patients in most large retrospective series.[1,5,6] Pelvic desmoid tumors are the rarest of all desmoid tumors.

A novel medical approach to these tumors, described by Waddell and Gerner[7] in 1980, was based on observations of spontaneous regression of a desmoid tumor in a woman at menopause[6] and regression of a large desmoid tumor in a male patient being treated with nonsteroidal anti-inflammatory drugs for an unrelated problem.[7] Subsequently, the use of tamoxifen and sulindac (a long-acting analogue of indomethacin) to treat patients with desmoid tumors has been associated with partial and complete responses in several nonrandomized retrospective studies.[8,9] Although strong evidence of the effectiveness of this regimen is debatable, the low morbidity associated with these drugs makes the option of a therapeutic trial of antiestrogen and nonsteroidal anti-inflammatory agents appealing. The following case illustrates a response to antiestrogens and anti-inflammatory treatment objectively measured by computed tomographic monitoring.

CASE REPORT

A 54-year-old white man experienced the development of urinary retention during hospitalization for a transient ischemic attack. The patient related a history of gradually worsening urinary hesitancy and occasional postvoid dribbling. He had been evaluated twice in the preceding 2 years with flexible sigmoidoscopy for rectal pain, which he described as "shooting." The stool had recently become flat and ribbonlike.

Physical examination revealed a soft abdomen free of masses or suspicious regions of fullness. On rectal examination, a large smooth mass was found deep within the pelvis on the left side, clearly pushing the rectum to the right. The tumor was thought to be contiguous with the left posterior prostate and came within 3 cm of the anal verge. The left lateral sulcus was obliterated.

Prostate-specific antigen was measured at 0.9 ng/dL. Transrectal ultrasonography demonstrated

*Present address: Abington Hospital, Medical Office Building, 1245 Highland Avenue, Abington, PA 19001-3781.

From the Departments of Urology and Diagnostic Radiology, Lahey Hitchcock Medical Center, Burlington, Massachusetts

Reprint requests: Leonard N. Zinman, M.D., Department of Urology, Lahey Hitchcock Medical Center, 41 Mall Road, Burlington, MA 01805

Submitted: October 12, 1995, accepted (with revisions): November 27, 1995

0090-4295/96/$15.00
PII S0090-4295(96)00026-X

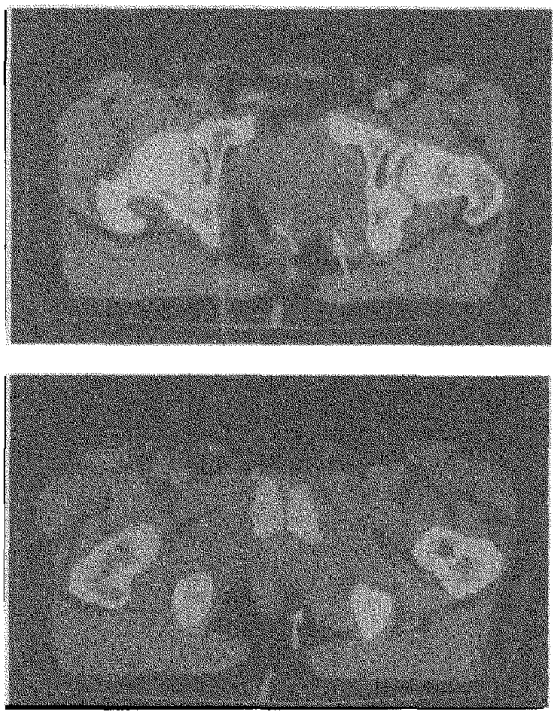

FIGURE 1. *(A) June 30, 1991. A large bilobed mass measuring 9.8 by 10 cm is seen in the left side of the pelvis (straight arrow) displacing the air-filled rectum (curved arrow). (B) Enlarged left obturator internus muscle (arrow) represents extension of tumor.*

a large heterogeneous mass contiguous with the prostate. The mass was too large to be imaged precisely using this modality. Scattered areas of calcification were noted. Transrectal ultrasound-guided biopsy demonstrated fibroblastic tissue and degenerating skeletal muscle. Neither barium enema study nor excretory urography (IVU) demonstrated a serious abnormality beyond extrinsic compression.

Contrast-enhanced computed tomography of the abdomen and pelvis (Fig. 1A) revealed a 10.0 by 9.8-cm heterogeneous mass in the pelvis measuring between 40 and 60 HU. The mass appeared to involve the pelvic musculature (Fig. 1B), specifically the left internal obturator and levator ani muscles.

Because of concern that the transrectal biopsies reflected inadequate sampling of the mass, the patient was taken to the operating room where multiple core biopsies were obtained both transrectally and transperineally. Simultaneous cystoscopy demonstrated minimal deviation of the membranous and prostatic urethra to the right. No mucosal or submucosal lesions were identified. Repeated biopsies yielded bland fibroblastic and poorly cellular material. Review of the slides by several pathologists suggested that this tumor was consistent with fibromatosis.

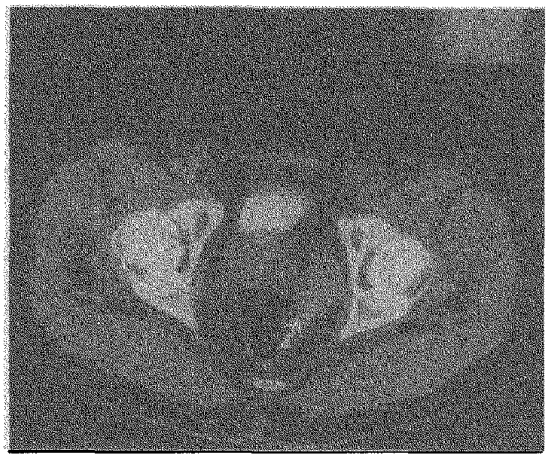

FIGURE 2. *January 18, 1994. The mass (arrow) is reduced in size and measures 3.2 by 6.0 cm.*

After much discussion, a regimen of orally administered sulindac, 150 mg twice a day, and tamoxifen, 80 mg twice a day, was started on a trial basis. Within 1 month, the patient reported an improvement in his ability to urinate as well as in the caliber of his stools.

Serial rectal examinations and computed tomography of the pelvis were performed at regular intervals. No significant change in the size of the lesion was noted for 30 months (Fig. 2), at which time the pelvic desmoid tumor began to become smaller. The tumor was reduced in size to 4.2 by 2.2 cm 54 months (Fig. 3) after initiation of treatment. No abnormality was appreciated on digital rectal examination, and the patient is currently asymptomatic.

COMMENT

Desmoid tumors were first described more than 160 years ago.[10] Because of the rarity of this neoplasm, however, clinical data are meager, and the reported efficacy of various therapies is almost anecdotal. Systematic retrospective studies are difficult to perform because desmoid tumors are not routinely included in most tumor registries.

Histologically characterized by abundant collagen and sheets of well-differentiated, uniform fibroblasts, these tumors typically have an infiltrating border and cause extensive morbidity by local invasion.[2,11] Desmoid tumors are estimated to occur in 2 to 4 persons per million a year.[5] They are more common in young women, and they are known to be associated with Gardner's syndrome.

The largest clinical series to date was reported by Reitamo *et al.*,[6] who manually screened 386,080 pathologic reports to identify 89 cases pathologically reconfirmed at the University of Helsinki. Among these patients, significantly higher rates of tumor growth were seen in women

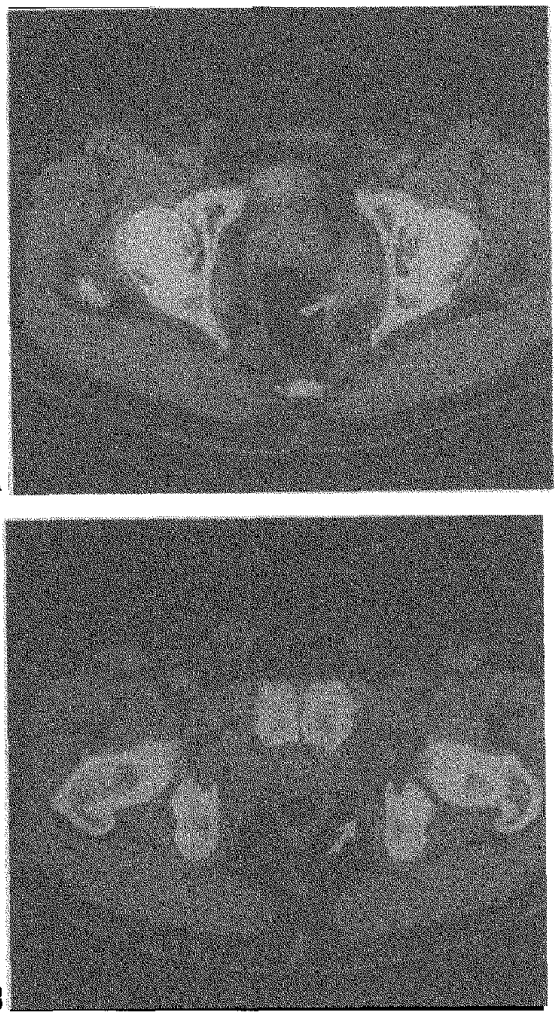

FIGURE 3. *(A) January 3, 1995. The mass (arrow) is further reduced in size and measures 2.2 by 4.2 cm. (B) The left obturator internus muscle (arrow) has returned to normal size.*

of reproductive age compared with premenarche or postmenopausal female patients or male patients. In addition, higher levels of estradiol receptors were found in the cytosol of the tumor compared with healthy adjacent tissue. Other investigators[12] have confirmed this finding. This fact lends credence to the concept that estrogen is somehow trophic to desmoid tumors.

The frequency of recurrence in the Helsinki series[6] did not differ whether the tumor was completely or incompletely resected. Recurrence was more likely when the tumor was in an extra-abdominal location than when it was an abdominal tumor. Children tended to have a higher rate of recurrence than adults in this report[6] as well as in other series.[11,13] Most recurrent tumors are detected within 3 years of original resection. Reported local recurrence rates vary widely despite total resection of the tumor.[1] Incomplete resection, however, is associated with even higher rates of recurrence in most series,[14–16] but some series[4] and case reports[17] suggest this to be an inconsistent finding.

The role of radiotherapy in the treatment of patients with unresectable or recurrent disease, toward the end of achieving local control of the tumor, is well documented.[1,18,19] Large treatment portals must be used because desmoid tumors notoriously have microscopic extension beyond the margin that might be indicated by computed tomography or magnetic resonance imaging, but the morbidity consistent with 50 to 55 Gy delivered to a large pelvic or abdominal field must be considered. Most of the radiotherapy experience has been directed toward nonvisceral sites and has been thought to be of doubtful benefit.[13,16,20] In fact, the Helsinki series[6] suggested that radiation therapy increased the rate of recurrence. Cytotoxic chemotherapy also has a limited role. Objective remissions of varying duration and degree have been reported with many agents, but the number of patients treated with any one protocol is low.[3] Weiss and Lackman[21,22] treated 8 patients with a low-dose vinblastine and methotrexate regimen that resulted in partial remission in 4 patients. Complete remission occurred in 2 patients, 1 of whom was a woman with a large pelvic desmoid tumor.

The use of antiestrogen and nonsteroidal antiinflammatory drugs in the treatment of patients with desmoid tumors is based on an apparent estrogen sensitivity of these neoplasms and on the surprising observation of total regression of a single recurrent desmoid tumor of the sternum in a patient taking indomethacin for radiation-induced pericarditis. Waddell and Kirsch[23] subsequently recorded major regression in 6 of 7 patients treated with antiestrogens (testolactone or tamoxifen) and sulindac. The authors postulated that the latter drug acted synergistically with estrogen blockade by inhibiting prostaglandin and cyclic adenosine monophosphate synthesis. Subsequent dramatic reports[24,25] of tumor regression in patients given similar therapy have been reported, with minimal associated toxicity.

Our approach to the treatment of the patient with this large pelvic tumor was based on the knowledge of the natural history of desmoid tumors and the dictum "first do no harm." It is generally agreed that the primary treatment of a patient with a desmoid tumor is complete surgical excision. Resection of this mass was certainly possible, as was reasonable reconstruction of the rectum and bladder if necessary. Given the potentially high rate of recurrence, however, a trial of unproved but minimally toxic therapy, under careful supervision and monitoring, was preferable to surgical intervention.

The classification of desmoid tumors as benign entities and not as low-grade sarcomas has been criticized. Inclusion of these neoplasms in tumor registries would enable more effective gathering of clinical data and might do much to improve our current understanding of these unusual neoplasms.

REFERENCES

1. Acker JC, Bossen EH, and Halperin EC: The management of desmoid tumors. Int J Radiat Oncol Biol Phys **26**: 851–858, 1993.

2. Khorsand J, and Karakousis CP: Desmoid tumors and their management. Am J Surg **149**: 215–218, 1985.

3. Gansar GF, and Krementz ET: Desmoid tumors: experience with new modes of therapy. South Med J **81**: 794–796, 1988.

4. Miralbell R, Suit HD, Mankin HJ, Zuckerberg LR, Stracher MA, and Rosenberg AE: Fibromatoses: from postsurgical surveillance to combined surgery and radiation therapy. Int J Radiat Oncol Biol Phys **18**: 535–540, 1990.

5. Welling RE, Hermann ME, and Kasper GC: Experience with desmoid tumor in a community teaching hospital. J Surg Oncol **49**: 113–115, 1992.

6. Reitamo JJ, Scheinin TM, and Häyry P: The desmoid syndrome. New aspects in the cause, pathogenesis and treatment of the desmoid tumor. Am J Surg **151**: 230–237, 1986.

7. Waddell WR, and Gerner RE: Indomethacin and ascorbate inhibit desmoid tumors. J Surg Oncol **15**: 85–90, 1980.

8. Klein WA, Miller HH, Anderson M, and DeCosse JJ: The use of indomethacin, sulindac, and tamoxifen for the treatment of desmoid tumors associated with familial polyposis. Cancer **60**: 2863–2868, 1987.

9. Easter DW, and Halasz NA: Recent trends in the management of desmoid tumors. Summary of 19 cases and review of the literature. Ann Surg **210**: 765–769, 1989.

10. MacFarlane J: *Clinical Reports on the Surgical Practice of the Glasgow Royal Infirmary*. Glasgow, D. Robertson, 1832, p 63. Cited by Easter and Halasz.[9]

11. Posner MC, Shiu MH, Newsome JL, Hajdu SI, Gaynor JJ, and Brennan MF: The desmoid tumor. Not a benign disease. Arch Surg **124**: 191–196, 1989.

12. Lim CL, Walker MJ, Mehta RR, and Das Gupta TK: Estrogen and antiestrogen binding sites in desmoid tumors. Eur J Cancer Clin Oncol **22**: 583–587, 1986.

13. Lopez R, Kemalyan N, Moseley HS, Dennis D, and Vetto RM: Problems in diagnosis and management of desmoid tumors. Am J Surg **159**: 450–453, 1990.

14. Häyry P, Reitamo JJ, Tötterman S, Hopfner-Hallikainen D, and Sivula A: The desmoid tumor. II. Analysis of factors possibly contributing to the etiology and growth behavior. Am J Clin Pathol **77**: 674–680, 1982.

15. Russell WO, Cohen J, Enzinger F, Hajdu SI, Heise H, Martin RG, Meissner W, Miller WT, Schmitz RL, and Suit HD: A clinical and pathological staging system for soft tissue sarcomas. Cancer **40**: 1562–1570, 1977.

16. McKinnon JG, Neifeld JP, Kay S, Parker GA, Foster WC, and Lawrence W Jr: Management of desmoid tumors. Surg Gynecol Obstet **169**: 104–106, 1989.

17. Ito T, Nakahara H, Ikeda M, Kuranishi F, Ogawa Y, Kuroda Y, and Watanabe K: Intra-abdominal mesenteric desmoid tumor. South Med J **83**: 330–331, 1990.

18. Keus R, and Bartelink H: The role of radiotherapy in the treatment of desmoid tumours. Radiother Oncol **7**: 1–5, 1986.

19. McCollough WM, Parsons JT, van den Griend R, Enneking WF, and Heare T: Radiation therapy for aggressive fibromatosis. The experience at the University of Florida. J Bone Joint Surg Am **73**: 717–725, 1991.

20. Rock MG, Pritchard DJ, Reiman HM, Soule EH, and Brewster RC: Extra-abdominal desmoid tumors. J Bone Joint Surg Am **66**: 1369–1374, 1984.

21. Weiss AJ, and Lackman RD: Therapy of desmoid tumors and related neoplasms. Compr Ther **17**: 32–34, 1991.

22. Weiss AJ, and Lackman RD: Low-dose chemotherapy of desmoid tumors. Cancer **64**: 1192–1194, 1989.

23. Waddell WR, and Kirsch WM: Testolactone, sulindac, warfarin, and vitamin K1 for unresectable desmoid tumors. Am J Surg **161**: 416–421, 1991.

24. Thomas S, Datta-Gupta S, and Kapur BM: Treatment of recurrent desmoid tumours with tamoxifen. Aust NZ J Surg **60**: 919–921, 1990.

25. Eagel BA, Zentler-Munro P, and Smith IE: Mesenteric desmoid tumours in Gardner's syndrome—review of medical treatments. Postgrad Med J **65**: 497–501, 1989.