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Case Reports

Possible Therapeutic Role of Vitamin D_3 in Aggressive Fibromatosis

Yildiz Ferah[1], Kars Ayse[2], Cengiz Mustafa[1], Selek Ugur[1], Gurkaynak Murat[1] and Atahan I. Lale[1]

[1]Department of Radiation Oncology and [2]Department of Medical Oncology, Hacettepe University Faculty of Medicine, 06100, Ankara, Turkey

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Desmoids, also known as aggressive fibromatoses, are locally invasive tumors that are intermediate in their biological behavior that lies between benign fibrous proliferations and low-grade fibrosarcomas. In this report, we present a case of a young female patient with a huge tumoral mass located in the right shoulder region that recurred after total resection and was resistant to radio-chemo-hormonal therapy. Eventually, she responded to 1,25-$(OH)_2$-vitamin D_3 treatment.

Key words: aggressive fibromatosis – vitamin D_3

INTRODUCTION

Aggressive fibromatosis is a benign exuberant proliferation of fibroblasts within a collagen matrix that infiltrates and destroys local tissues. Surgery remains the treatment of choice, and local control rates vary considerably depending on the margin status. Overall recurrence rate with surgery alone is reported to be around 40% (1). Higher local control rates are achieved with the addition of postoperative radiotherapy and are reported to be around 94% and 75% for tumor-free and tumor-positive margins, respectively (2). Irradiation alone is usually indicated in patients in whom the primary or the postsurgical recurrent tumor is resectable at the cost of considerable cosmetic or functional deficit and in medically inoperable patients. Local control rates with radiotherapy alone are reported to be in the range of 70–80% (2).

The potential morbidity from surgery and radiotherapy and the high local recurrence rates have led investigators to evaluate the role of systemic treatment with drugs such as tamoxifen, toremifene or nonsteroidal anti-inflammatory drugs or biological agents such as interferon or retinoic acid (3). 1,25-$(OH)_2$-vitamin D_3 has been shown to inhibit proliferation and increase c-myc expression in fibroblasts (4) and to induce apoptosis in several tumor cell lines (5–9). It is used in chronic myeloproliferative disorders based on the information that active metabolites of vitamin D_3 inhibit collagen deposition by both down regulating its synthesis and increasing its degradation (10). Herein we report a case of a young female patient treated with 1,25-$(OH)_2$-vitamin D_3 for local recurrence and progression of aggressive fibromatosis in the shoulder region following surgery and two courses of radiotherapy, hormonal therapy and chemotherapy.

For reprints and all correspondence: Yildiz Ferah, Hacettepe University Faculty of Medicine, Department of Radiation Oncology, 06100, Ankara, Turkey. E-mail: fyildiz@hacettepe.edu.tr

CASE REPORT

A 26-year-old female patient was referred to the Department of Radiation Oncology, Hacettepe University Faculty of Medicine with complaints of severe pain and impaired mobility in the right shoulder, in April 1996. She had a history of a traffic accident with a fracture of the right clavicle 3 years earlier. She had undergone a fixative surgical operation for the fracture. In October 1994, she had to be reoperated for an $11 \times 9 \times 3$ cm mass located on the formerly fixed right clavicle, and a gross total excision was performed. The pathology specimen revealed dense collagenous material interspersed with spindle cells and typical fibroblasts without mitosis and was diagnosed as aggressive fibromatosis. She was followed up for 1 year without any intervention at the end of which she developed a $3 \times 6 \times 8$ cm painful mass located in the right pectoralis muscle along with an axillary lymphadenopathy. No further surgery was planned, since it would be mutilating. The tumor bed was irradiated, leaving a 3-cm safety margin using 6-MV photon beams up to a total dose of 60 Gy with conventional daily fractionation. A concomitant dose of 30 mg/day of tamoxifen was prescribed. Following radiotherapy, she continued to receive the same dose of tamoxifen for a further 6-month period. A minimal regression was recorded on MRI scans 3 months after irradiation. In June 1998, MRI scans revealed a huge $14 \times 7.5 \times 12$ cm mass infiltrating the muscular compartments, extending up to the thoracic inlet, obliterating the intervertebral foramina of the lower cervical and upper thoracic

spine and entering into the spinal canal and circumscribing the right brachial plexus, the internal carotid artery and the subclavian artery and veins. A course of 120 mg/day toremifene therapy, a triphenylene derivate, was administered for 2 months without any response. A second course of radiotherapy with shielding of the previous treatment portals up to a total dose of 60 Gy was administered between October and December 1998. Two cycles of VAC (vincristine, actinomycin D and cyclophosphamide) combination were administered concomitantly with radiotherapy and a third cycle following radiotherapy. Peripheral neuropathy precluded further chemotherapy after January 1999. In March 1999, further progression of the tumor was detected by both physical examination and MRI scans (Fig. 1a and b). Progression was apparent especially in the distal part of the tumor lying on the apical part of right lung parenchyma. Moreover, at this time, the tumor showed an infiltrative pattern. Tumor dimensions were calculated to be $16 \times 7.7 \times 12$ cm. Since no response was achieved with these treatment modalities, she was administered 0.5 mcg/day of calcitriol (1,25-$(OH)_2$-vitamin D_3), which was reported to be effective in the treatment of myeloproliferative disorders. In December 1999, nearly 8 months after vitamin D administration, MRI scans revealed a $10 \times 6.5 \times 3$ cm mass. In May 2000, while she was still receiving vitamin D_3 treatment, further regression of the tumor was recorded. Tumor dimensions were $9 \times 6.5 \times 3$ cm on MRI scans (Fig. 2). Symptomatic relief was also apparent. In June 2001, she gave a healthy birth. There was no deleterious effect of the pregnancy on disease outcome. Though there was a brief interruption in vitamin D_3 therapy for 3–4 months after delivery, she continued to receive the medication subsequently. Both physical examination and MRI scans showed further regression in November 2002. Tumor dimensions were calculated to be $7 \times 4.5 \times 3$ cm (Fig. 3).

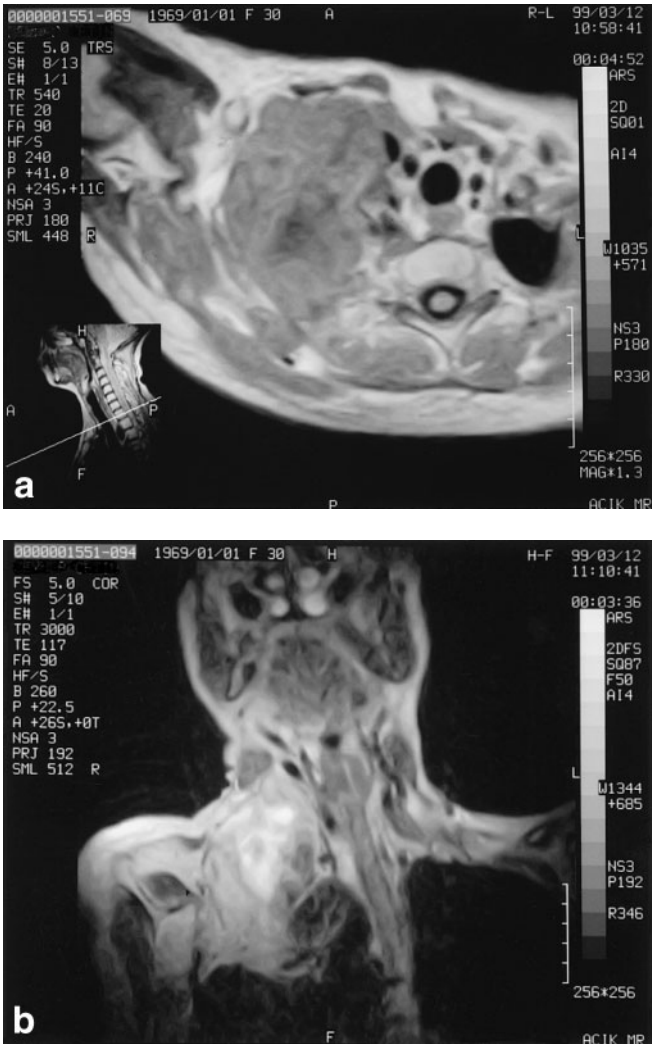

Figure 1. (a) Axial and (b) coronal MRI sections before calcitriol administration, demonstrating a huge mass infiltrating muscular compartments, extending to the thoracic inlet, obliterating the intervertebral foramina of the lower cervical and upper thoracic spine, and entering the spinal canal and circumscribing the right brachial plexus, the internal carotid artery and the subclavian artery and veins.

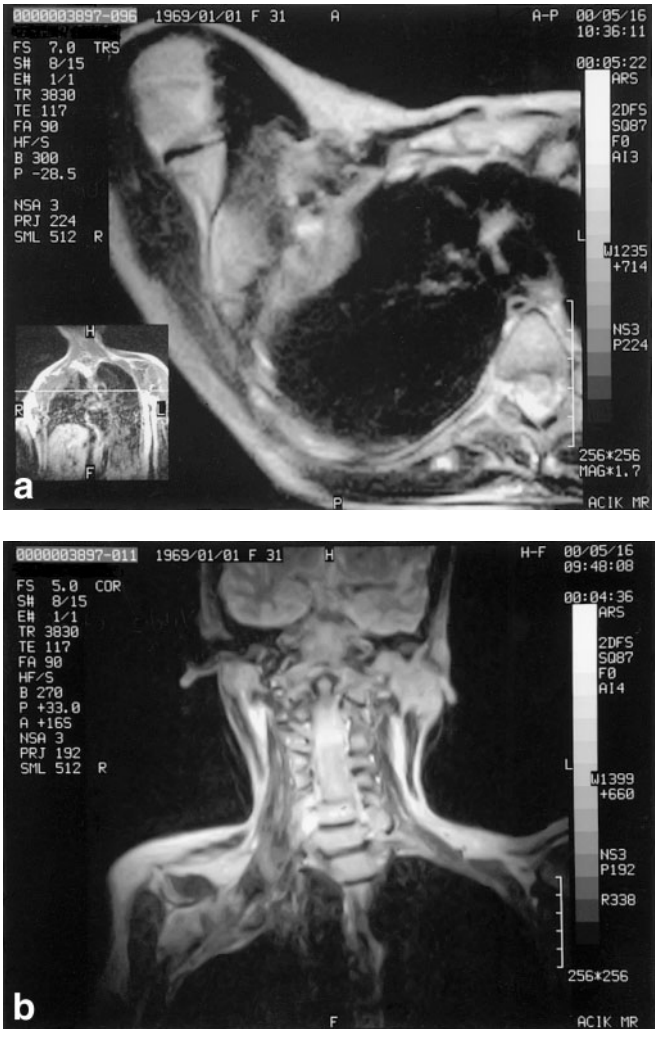

Figure 2. (a) Axial and (b) coronal MRI sections 14 months after calcitriol treatment. An apparent regression is evident.

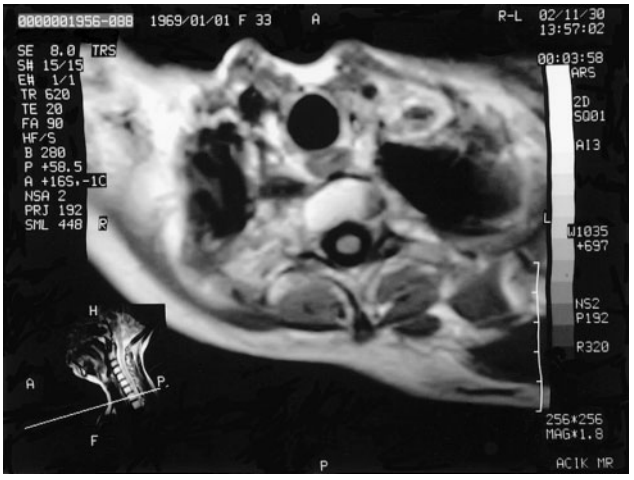

Figure 3. Axial MRI section, 44 months after calcitriol treatment.

Serum calcium concentrations were checked regularly during vitamin D_3 treatment, and no decrease was detected in the serum concentrations in any of these samples.

DISCUSSION

Treatment of aggressive fibromatosis usually comprises a wide local excision with or without radiotherapy. Patients with recurrent, unresectable tumors often die due to the locally aggressive nature of the tumor. Therefore, effective medical treatments are urgently needed in these patients. Reports in literature on the utility of chemotherapy have been anecdotal and confined to small series. In one of the largest series, Azzarelli et al. reported a 40% objective response rate and a 67% actuarial progression-free survival rate at 10 years with low-dose methotrexate and vinblastine chemotherapy in 30 patients with advanced inoperable tumors (11). On the other hand, the response rates to doxorubicin-based chemotherapy regimens were reported to be in the range of 40–67% (12,13). However, the toxicity, mainly hematologic toxicity, precludes the administration of optimum dose and cycles of chemotherapy. Efforts to seek effective but less toxic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) and antiestrogen treatments. Estrogen receptors (ER) in desmoid tumors have long been demonstrated in patients with familial adenomatous polyposis; although, the receptor levels were low (14,15). The presence of antiestrogen binding sites distinct from ERs are claimed to be responsible for the response to antiestrogen treatment, especially in ER-negative patients. Antiestrogen treatments such as tamoxifen, toremifene, raloxifene, progesterone, testolactone and goserelin are reported to produce 33–60% objective response rates (16–19).

The use of NSAIDs in the treatment of desmoid tumors was based 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 (20). There is clear evidence that endogenous prostaglandin synthesis plays a role in neoplastic growth. NSAIDs such as sulindac or indomethacin produce 37–57% objective response rates, either as partial or complete responses (19,21,22). In a report by Hansman et al., patients receiving sulindac in combination with high-dose tamoxifen show 69% complete or partial response rates (23).

In the present case, antiestrogen treatment and three courses of VAC chemotherapy failed to produce any objective response, and the patient was prescribed vitamin D. Besides the well-known effects on classical target tissues such as bones, kidneys, intestines and parathyroid, it has been demonstrated that vitamin D plays an important role in the regulation of cell growth and differentiation in cells other than its classical targets. The antiproliferative action of 1,25-$(OH)_2$-vitamin D_3 was first demonstrated in mouse myeloid leukemia cells in 1981 (5). It has subsequently been shown to inhibit the growth of osteosarcoma, breast carcinoma, colonic carcinoma, prostate carcinoma, hepatoblastoma and malignant melanoma cell lines (6,7,9,24,25). Effects of the active metabolites of vitamin D on the induction of apoptosis have been reported to be mediated by either the induction of expression of cyclin-dependent kinase inhibitors such as $p21^{WAF/CIPI}$ (8) and $p27^{KIPI}$ (26) or TGF-β1 (27). In addition, the c-myc proto-oncogene was shown to be down regulated by vitamin D_3 in psoriatic fibroblasts (4). The role of 1,25-$(OH)_2$-vitamin D_3 in the control of bone marrow collagen deposition in the treatment of myelofibrosis has been reported by several authors (10,28). It is suggested that 1,25-$(OH)_2$-vitamin D_3 inhibits the formation of collagen I and III in bone marrow and increases their degradation by inhibiting the proliferation of megakaryocytes that promote collagen synthesis and increasing the number and activity of monocytes and macrophages that possess collagenase activity (29). The present case experienced tumor progression after gross total surgical excision and was resistant to radiotherapy, chemotherapy and hormonal therapy. Based on the previous experience with 1,25-$(OH)_2$-vitamin D_3 in chronic myeloproliferative disorders following the second course of radiotherapy, 1,25-$(OH)_2$-vitamin D_3 was prescribed, and a gradual and continuous regression was detected by both physical examination and MRI scans. Regression of the tumor can be attributed to the second course of radiotherapy since response to radiotherapy may be delayed by as much as 8–27 months (30,31). However, in this case, a marginal and out-field recurrence was detected 4 months after the second course of radiotherapy. On the other hand, several studies have demonstrated that vitamin D_3 and its active analogues can be effectively combined with chemotherapeutic drugs such as adriamycin as well as ionizing radiation (32,33). The interaction is reported to be at least additive (9). Based on the findings in the present case, the effect of vitamin D can be considered to be an independent action or an additive action after radiotherapy.

In conclusion, though it is difficult to reach definitive conclusions regarding the efficacy of vitamin D in aggressive fibromatosis based on the findings in a single patient, we are of the opinion that it would be worthwhile to conduct further studies on this aspect.

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