Effective treatment of multifocal aggressive fibromatosis with low-dose chemotherapy

Kudret Çağlar[1], Hasan Özyönüm[2], Minel Akalın[3], Sevim Balcı[4]

[1]Pediatric Oncology Unit, and Departments of [2]Pediatrics, and [3]Pathology, Dr. Burhan Nalbantoğlu State Hospital, Nicosia, North Cyprus, and [4]Clinical Genetics Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Cağlar K, Özyönüm H, Akalın M, Balcı S. Effective treatment of multifocal aggressive fibromatosis with low-dose chemotherapy. Turk J Pediatr 2006; 48: 365-368.

Desmoid tumor (aggressive fibromatosis), as a member of a group of borderline neoplasms, is a rare tumor of fibroblastic origin that remains difficult to treat. Treatments with surgery, radiotherapy and different medical protocols including interferon (IFN)-α, hormonal agents such as tamoxifen (anti-estrogen) as well as non-steroidal anti-inflammatory drugs and low-dose antineoplastic agents have been reported. In this report we describe a new patient with multifocal aggressive fibromatosis who was successfully treated with low-dose chemotherapy consisting of methotrexate and vinblastine.

Key words: aggressive fibromatosis, low dose chemotherapy, pediatric.

Desmoid tumor (aggressive fibromatosis), with an annual incidence of 0.2-0.5 per 100,000 population, is a rare borderline tumor originating from deep musculo-aponeurotic structure[1-3]. Aggressive fibromatosis is a deep-seated, poorly circumscribed, benign tumor with an infiltrative-like pattern toward mesenchymal tissues[1-5]. Recurrent and local aggressive disease may threaten the life of the patient[1]. Aggressive fibromatosis occurs anywhere in the body with a high predilection of limb, girdles and proximal extremities, neck, trunk, abdominal wall, bowel wall and mesentery[1-10]. By nature, it generally cannot be separated from the connective tissues with a free surgical margin, and as a result, it has high potential for local recurrence[1-10]. Treatments with surgery alone or combined surgery and radiotherapy are not producing successful results (60%)[2,4]. In surgical series, recurrence rate in desmoid tumor was reported as ranging between 39% to 79%[4]. Different medical treatment protocols have been reported in the literature. These include the use of interferon (IFN)-α, hormonal agents such as tamoxifen (anti-estrogen), as well as non-steroidal anti-inflammatory drugs and low-dose antineoplastic agents. In fact, effective medical treatment with less toxicity has not been described to date.

In this report, we describe a new patient with multifocal aggressive fibromatosis treated with a low-dose cytotoxic chemotherapy.

Case Report

A 17-year-old mentally- and motor-retarded girl of nonconsanguineous parents with a two-year history of perianal, plantar and pelvic masses was admitted to a university hospital in 2001. After performing incisional biopsy, the patient, with the diagnosis of multicentric desmoid tumor, was planned to undergo operation for complete resection of lesions. Since it was thought that excision with a wide margin would be adequate local treatment of the desmoid tumors, she was hospitalized for the preparation of a surgical intervention. During the surgery, the fifth toe of her left foot was amputated and masses on the perianal and pelvic skin were totally resected. Upon histopathological examination, a diagnosis of desmoid tumor (fibromatosis) was made with no mention about surgical margins.

One year later, she was admitted to our hospital with recurrent lesions on the operation zones. An extensive tumor resection was planned at

the Department of Surgery, but due to the family's refusal of operation, she was referred to our department. On the initial physical examination, multiple, vascular solid lesions originating from pelvic skin, perianal region and the left amputated toe area were detected. They were all originated from the operation scar, with dimensions of 5x20 cm (pelvic wall), 3x4 cm (perianal) and 1x1 cm (left amputated toe) (Fig. 1). It was observed that the child had a friendly demeanor and smiled frequently. We also noted micromelia, micrognathia and mental and growth retardation. We learned from her medical history that she was born with congenital scalp defect and cataract. On the laboratory examination, blood counts were within normal limits. Renal and liver function tests and routine serum biochemistry tests results were normal. Echocardiography was within normal limits. Chromosomal analysis from peripheral blood yielded 46-XX. FISH study for Angelman and Williams syndromes were normal. To confirm the diagnosis, a punch biopsy was done from the mass on pelvic skin. Pathological examination revealed poorly circumscribed lesions consisting of elongated slender spindle-shaped cells of uniform appearance surrounded and separated by collagen. Fibroblastic cells without atypical or hyperchromatic nuclei were seen. Secondary degenerative changes in the lesion (microhemorrhage, inflammation, etc.) were not detected. These histopathologic findings confirmed the diagnosis of fibromatosis (Fig. 2). Both abdominal ultrasonography (USG) and computerized tomography (CT) demonstrated that all lesions originated from the previous operation scars. We decided to treat the patient with IFN-α-2c using the dose of 3 million IU three times weekly[6]. At the end of the three months of this trial there was no evidence of disease regression. Contrary to the expectations, the lesion that originated from the pelvic skin had enlarged. Low dose methotrexate (30 mg/m^2, max 50 mg, IV) and vinblastine (6 mg/m^2, max 10 mg, IV) was given every seven days with parental consent[2]. With this treatment, the lesions remarkably regressed (Fig. 3).

Discussion

Desmoid tumor (aggressive fibromatosis), with its slow-growing infiltrative nature and locally aggressive behavior, remains difficult to treat. According to previous reports, the treatment of unresectable desmoid tumors is usually palliative[1-10]. En-bloc surgery with negative surgical margin, with or without radiation therapy is the primary treatment of most

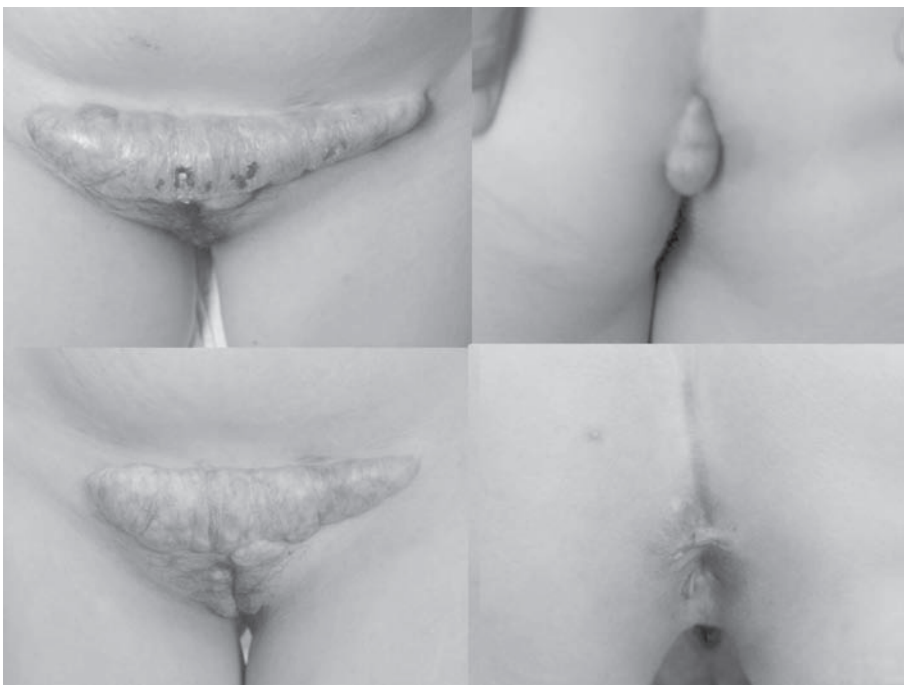

Fig. 1. Response of lesions to low-dose chemotherapy was clearly seen in a two-month period.

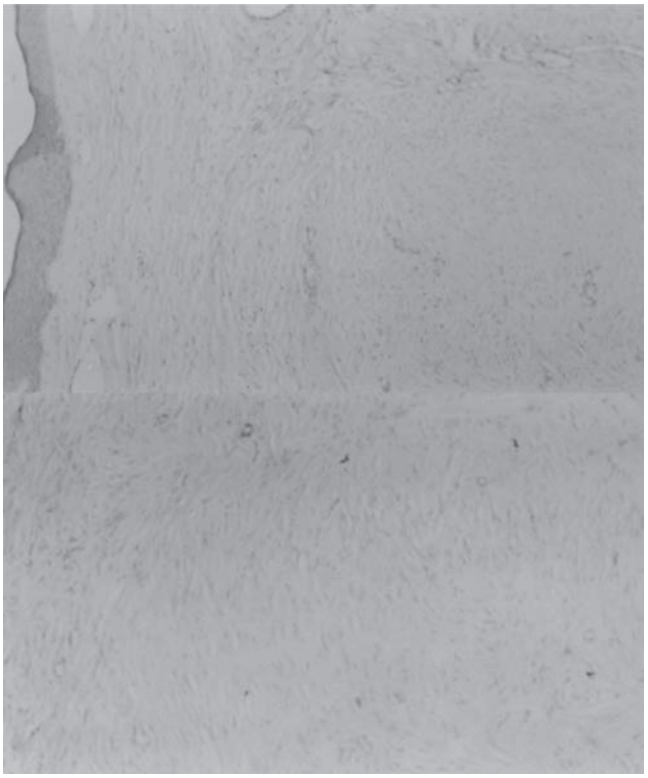

Fig. 2. Pathological findings of the lesion.

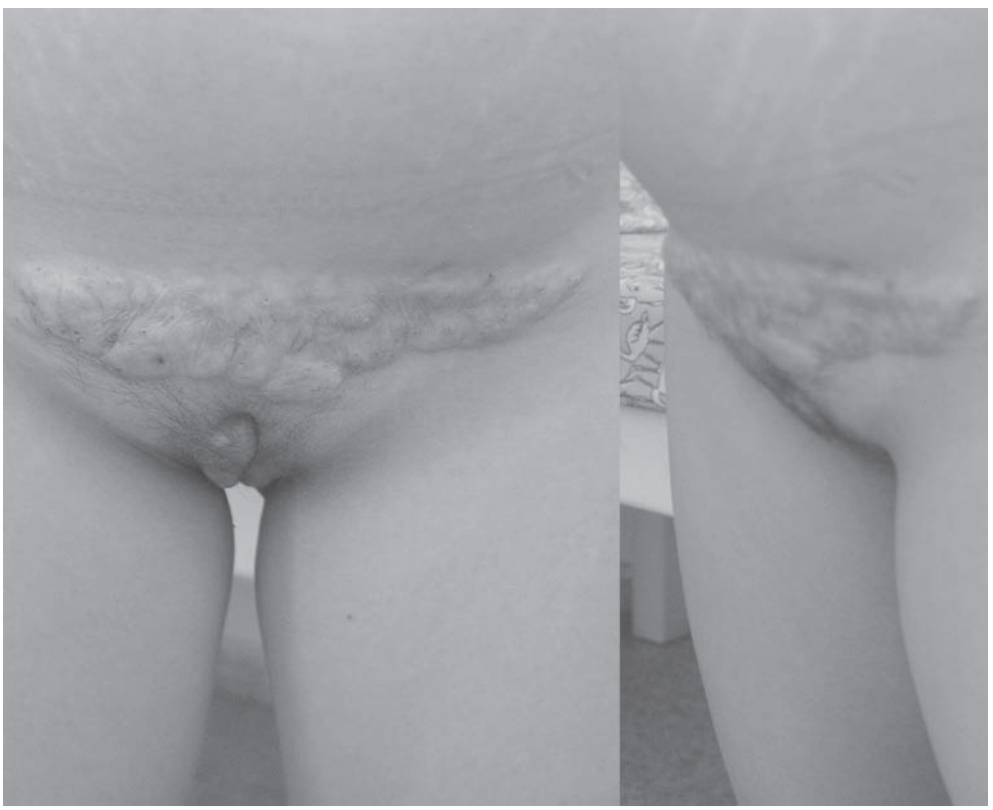

Fig. 3. Significant resolution of lesions at the end of 12 months of treatment.

desmoid tumors[1-10]. In patients with recurrent and unresectable disease, IFN-α, hormonal agents such as tamoxifen (anti-estrogen), as well as non-steroidal anti-inflammatory drugs, have been used previously[1-10]. To the best of our knowledge, effective medical treatment with less toxicity has not been described to date[1-10]. In the recent studies, chemotherapy regimen has been confirmed to have an impact on progression of disease[1-4]. Despite the benign pathology, local invasion capacity and frequent recurrences of the disease, some authors and some institutions consider them equivalent to low-grade soft tissue sarcomas[1,2,8].

Additional findings like micromelia, micrognathia, mental and growth retardation, congenital scalp defect and cataract in the presented case may be the characteristic symptoms of a new, previously undescribed syndrome. We could not detect any abnormality on chromosomal studies. FISH studies for Angelman and Williams syndromes excluded these two diagnoses.

After two months of treatment with low-dose methotrexate (30 mg/m^2, max 50 mg, IV) and vinblastine (6 mg/m^2, max 10 mg, IV) given every seven days, perianal lesions and those on the left amputated toe area showed complete regression (Fig. 1). The lesion on the pelvic skin had regressed partially (approximately 50% reduction in size) (Fig. 1). At the end of 12 months of treatment with low-dose chemotherapy, the pelvic lesion reduced approximately 80% in size (Fig. 3). The patient is now nine months into her follow-up for recurrence or progress of the disease. At the last follow-up there was no evidence of local recurrence or progress of the disease.

Based on our experience in this presented case we can say that aggressive fibromatosis (desmoid tumors) can be treated successfully with low-dose methotrexate and vinblastine given every seven days. Low-dose methotrexate and vinblastine treatment can be an alternative to the most demanding surgical or radiation therapy in cases of unresectable and multifocal disease.

REFERENCES

1. Okuno SH, Edmonson JH. Combination chemotherapy for desmoid tumors. Cancer 2003; 97: 1134-1135.
2. Azzarelli A, Gronchi A, Bertulli R, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer 2001; 92: 1259-1264.
3. Goy BW, Lee SP, Eilber F, et al. The role of adjuvant radiotherapy in the treatment of resectable desmoid tumors. Int J Radiat Oncol Biol Phys 1997; 39: 659-665.
4. Ballo MT, Zagars GK, Pollack A, Pisters PW, Pollack RA. Desmoid tumor: prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. J Clin Oncol 1999; 17: 158-167.
5. Kamath SS, Parsons JT, Marcus RB, Zlotecki RA, Scarborough MT. Radiotherapy for local control of aggressive fibromatosis. Int J Radiat Oncol Biol Phys 1996; 36: 325-328.
6. Leithner A, Schnack B, Katterschafka T, et al. Treatment of extra-abdominal desmoid tumors with interferon-alpha with or without tretinoin. J Surg Oncol 2000; 73: 21-25.
7. Gronchi A, Casali PG, Mariani L, et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. J Clin Oncol 2003; 21: 1390-1397.
8. Skene AI, Barr L, A'Hern RP, Fisher C, Meirion Thomas J. Multimodality treatment in the control of deep musculoaponeurotic fibromatosis. Br J Surg 1998; 85: 655-658.
9. Merchant NB, Lewis JJ, Woodruff JM, Leung DH, Brennan MF. Extremity and trunk desmoid tumors: a multifactorial analysis of outcome. Cancer 1999; 86: 2045-2052.
10. Spear MA, Jennings LC, Mankin HJ, et al. Individualizing management of aggressive fibromatoses. Int J Radiat Oncol Biol Phys 1998; 40: 637-645.