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Original Article

Desmoid tumour, a rare tumour in oncology practice: A case series and literature review

Erkan Erdur[1], Ferit Aslan[2]

[1]Department of Internal Medicine, Division of Medical Oncology, Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey
[2]Department of Medical Oncology, Yuksek Ihtisas University Medicalpark Ankara Batikent Hospital, Ankara,Turkey

Abstract

Aim: Desmoid tumors (DTs) are very rare tumors that grow gradually anywhere in the body they are locally aggressive, but with a low potential for metastasis. Very good results can be obtained with different combinations of treatments, such as surgery, chemotherapy, hormonal therapy, tyrosine kinase inhibitor therapy and radiotherapy. Case series even with a small number of patients are of considerable importance as experience with DTs limited. Therefore, in this study, we aimed to discuss the management of DTs with our case series.

Materials and Methods: In our study, 15 patients with DT, who were treated and followed up between January 2005 and January 2020 in two hospital medical oncology departments in Turkey, were evaluated.

Results: The median age of diagnosis of the patients was 34 (range 18-48) years. Seven (46.6%) of the patients were female and eight (53.4%) were male. Seven (46.6%) of the tumors were located in the abdominal wall, four (26.7%) were in the limbs three (20%) were in the intra-abdominal area, and one (6.7%) was in the chest wall. In terms of resectability, 14 (93.3%) were resectable, and one (6.7%) was unresectable. The five-year overall survival rate was 73.85%, and the average disease-free survival time until relapse was 35 (range 15-83) months in patients who relapsed. The two- and five-year relapse-free survival rates were 90.9% and 66.5%, respectively. The median progression-free survival (PFS) for first-line treatment was 25 (range 8.6-89.8) months. The median PFS for second-line treatment was seven (range 4.3-38.0) months. In the one patient who received third-line treatment, PFS was 8.3 months.

Conclusion: Frequent relapses in DTs are still the biggest problem in treating this disease. Although surgery treatment is the main treatment method used in desmoid tumors, controversy about adjuvant therapy after surgery continues, and new treatment modalities are required.

Keywords: Desmoid tumors; recurrence; sulindac; survival; tamoxifen

INTRODUCTION

Desmoid tumors (DTs) are extremely rare. With an annual incidence rate of 2–5 per 1,000,000, DTs account for approximately 3% of all soft tissue sarcomas and 0.03% of all malignancies (1). DTs are locally aggressive but with a low potential for metastasis; they occur with clonal fibroblastic tissue proliferation and can develop anywhere in the body. These tumors can regress spontaneously, or they can cause massive damage to tissues and organs with an aggressive course (2,3). The female/male ratio is approximately 2:1, and patients are usually between 15 and 60 years old. There is no ethnic trend (4).

Clinicopathologically, DTs are divided into two groups. The first group is sporadic and constitutes 85-90% of cases. The second group, which constitutes 10-15% of DTs, includes tumors related to familial adenomatous polyposis (FAP). The incidence of DTs in patients with FAP is about 13% (5). It is most common in the limbs and in the shoulder girdle, hip region, surgical scar areas, abdomen and thorax wall, head, neck and intra-abdominal areas. Although sporadic cases can be seen in any part of the body, FAP-related DTs are most commonly located in intra-abdominal areas (6).

The etiopathogenesis of DTs is unclear but is considered to be multifactorial. FAP, Gardner's syndrome, pregnancy and the use of oral contraceptives are contributory factors,although recurrent traumas are considered to be the most common cause of development (7-9).

The literature on DTs consists mostly of case series and retrospective evaluations. We aimed to share the clinical, follow-up and treatment results of 15 retrospective cases related to this rare tumour.

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Corresponding Author: Erkan Erdur, Department of Internal Medicine, Division of Medical Oncology, Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey **E-mail:** erdurerkan@gmail.com

MATERIALS and METHODS

This study is based on the medical records of 15 patients with a diagnosis of DT. who were treated in two medical centers and followed up between January 2005 and January 2020 . The patients were categorized on the basis of their surgical status, tumor location, treatments, recurrence and death status. Demographic characteristics and survival-related parameters were specified. Overall survival (OS) was defined as the time from diagnosis to death. Disease-free survival (DFS) was defined as the time from diagnosis to recurrence.

Statistical Analysis

Statistical package for the social sciences (SPSS) 18.0 software was used to estimate survival rate, and descriptive data were analysed using the same program. Kaplan-Meier curves and a log-rank test were used to analyse the survival data, and p-values of <0.05 were considered statistically significant.

RESULTS

Data on the 15 patients are summarized in Table 1. The median age of diagnosis was 34 (range 18–48) years. Seven (46.6%) of the patients were female, and eight (53.4%) were male; the male/female ratio was nearly 1:1.1. Seven tumors (46.6%) were located in the abdominal wall, four (26.7%) were in the limbs, three (20%) were in the intra-abdominal area and one (6.7%) in the chest wall.

At the time of diagnosis, 14 (93.3%) of the 15 patients were symptomatic, and the masses in the limbs and abdominal wall were the main reason for hospital admission, whereas abdominal pain was the reason for admission for patients with a tumor in the intra-abdominal area. In one patient with an intra-abdominal tumor, the mass was detected during routine tests.

In terms of resectability, 14 tumors (93.3%) were resectable, and one (6.7%) was unresectable. Seven (50%) R0, four (28.6%) R1, and three (21.4%) R2 resections were carried out. Postoperative radiotherapy was administered to three (21.4%) patients without R0 resection. Recurrence was observed in nine (14.2%) of the 14 patients who underwent surgery as an initial treatment. Surgical operations were performed again in four (44.4%) of the recurrent patients. While one (25%) of the patients who underwent recurrence surgery had surgery only, one (25%) patient received postsurgical radiotherapy and still continues to be followed up without relapse. The median DFS was 35 (range 15-83) months.

Five (55.6%) patients were given tamoxifen–sulindac, three (33.3%) were given dacarbazine–adriamycin and one (11.1%) was given methotrexate–vinorelbine as the first-line treatments in nine patients with relapse and unresectable treatment. The median PFS for first-line treatment was 25 (range 8.6–89.8) months. Of the six patients who received second-line treatment, three (50%) received imatinib, two (33.3%) received tamoxifen–sulindac and one (16.7%) received dacarbazine–adriamycin. The median PFS for second-line treatment was seven (range 4.3–38.0) months. One patient received imatinib as a third-line treatment; PFS was 8.3 months for this.

The median follow-up time was 52.6 (range 2.6–170.7) months. During the evaluation, five patients (33.3%) died, one (20%) of whom died owing to non-DT-related reasons. When all the patients were evaluated, the five-year survival rate was 73.85%. The two- and five-year relapse-free survival rates were 90.9% and 66.5%, respectively.

DISCUSSION

Although multimodal approaches such as surgical treatment, radiotherapy and pharmacological treatment can be used to treat DTs, discussion about the optimal management of DT continues, and no gold standard treatment method has been identified yet (10,11). The main difficulty in the treatment of these histologically benign tumors is that the probability of local recurrence is as high as 20-45% (12). The probability of recurrence increases with young age, extremity location, large tumor and positive surgical margins (13). Unpredictable clinical conditions, such as a high probability of local recurrence despite surgical treatment, an aggressive course that may develop despite surgery and radiotherapy and spontaneous regression without treatment suggest a watchful waiting strategy , but there is no standard on this subject yet (14). In a study of 426 cases by Salas et al., a watchful-waiting strategy was selected in 27 patients, and progressive disease was observed in only 20% of the patients during follow-up (15). In a study of 142 cases by Bonvalot et al., a watchful-waiting strategy was used in 83 patients. Surgical operations were performed in 59 patients. In the follow-up of these patients, five years of PFS was observed in 49% of patients who did not undergo surgery and 58% of patients who underwent surgery; no statistical difference was detected (16). In a study by Ballow et al., 70% of patients achieved disease-free survival for five years (17).

In our study, 14 (93.3%) of the 15 patients received surgery as an initial treatment. The two- and five-year relapse-free survival rates were 90.9% and 66.5%, respectively.

Radiotherapy is another local control method used in the treatment of DTs. This is a good local control option except for DTs located in the abdominal area. It can be used in initial therapy, especially in elderly patients who cannot tolerate surgery owing to additional comorbidity, in patients who refuse surgery, and in patients for whom surgery carries a high risk. Surgical R1 or R2 can be used as an adjuvant therapy in resected patients and as a neoadjuvant in unresectable disease as well as an alternative to high-risk surgery in relapsed patients. Radiotherapy is not an option for R0 resected tumors (19,20). In our study, radiotherapy was given to three patients who underwent surgery and could not achieve R0 resection and to one patient who developed recurrence and could not achieve R0 with relapse surgery. Of these

four patients, three (75%) continued to be followed up without relapse. The patient who received radiotherapy after surgery in relapse has been followed up for 20.1 months without relapse. This result is consistent with a study by Gentile et al., in which radiotherapy in addition to post relapse surgery was evaluated (20).

Systemic therapies are an option in cases of progression after adequate local treatment, in recurrences that are not suitable for local treatments, in the initial treatment of a growing or symptomatic intra-abdominal/mesenteric DT, and in symptomatic cases where the risk of surgical morbidity is high. Systemic treatment agents indicated by small case series and information from retrospective studies include hormonal treatments, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy agents and targeted therapies (21). Chemotherapy agents are especially used in inoperable, symptomatic and fast-growing tumors that are close to critical structures, in tumours that cannot be fully resected, and in tumors that are considered to have high morbidity. Doxorubicin/pegylated liposomal doxorubicin, dacarbazine and methotrexate-vinblastine/vinorelbine are the most common combinations. Some centres recommend the use of single-agent methotrexate and single-agent pegylated liposomal doxorubicin (22,23). Three of our patients with recurrent and non-resectable disease received dacarbazine plus adriamycin therapy as a first-line therapy. In these patients, the PFS achieved with chemotherapy was 25.7 (range 15.1-37.3) months. In second-line treatment, one patient received dacarbazine plus adriamycin; PFS in this patient was 7.03 months.

In the retrospective case series of 75 cases by Palassini et al., 80% of the patients had symptomatic improvement after 12 months of treatment, and 75 months of PFS was achieved in the patients with a combination of methotrexate plus vinblastine or vinorelbine. PFS was reported to be 136 months in the patients with an objective response (complete response and partial response) (24,25). One of our patients with recurrent and non-resectable disease received methotrexate plus vinorelbine treatment as the first-line treatment, and the PFS achieved with chemotherapy in this patient was 8.63 months.

Oestrogen receptor expression is high in DTs, and frequent pregnancy and female gender along with the use of antioestrogen therapy are thought to be risk factors for DT, which is characterized by the β-catenin pathway regulation of cycloxygenase-2 (COX2) inhibitors through the inhibition of COX2 or prostaglandins (26-30). Tamoxifen or toremifene alone or in combination with NSAIDs has been widely used owing to their limited toxicity and low cost (31). In a study by Brooks et al. of patients with progressive disease following local treatment, a response was obtained in 13 (65%) of 20 patients using tamoxifen (32). The data on anti-inflammatory drugs used as the sole agent came from studies conducted with a small number of patients from the 1980s to the present, which indicated moderate disease control rates. Indomethacin, meloxicam, sulindac and colchicine were the treatment agents used. One of the most striking studies is a retrospective examination by Tsukada et al. of 14 patients who used sulindac. In this study, disease control was achieved in 12 (85%) of the 14 patients (30,33). Promising results from both hormonal therapy and NSAIDs suggest the use of combination therapies. In a 134-case retrospective case series by Quast et al., 85% of patients were controlled with a combination of tamoxifen and sulindac. The response rate was reported to be the same for tumours accompanying FAP and sporadic tumours (30,34). In our study, five of the patients who were followed up were given a tamoxifen-sulindac combination as a first-line therapy. The median PFS achieved in these patients was 31.47 (range 13.2-89.8) months. As a second-line treatment, two patients received a tamoxifen-sulindac combination, and their PFS times were 5.33 and 38.0 months .

Receptor tyrosine kinases such as PDGFR and VEGFR, which are responsible for mesenchymal cell growth and angiogenesis, are highly expressed in DTs and are targeted areas in these tumours. Although prospective studies are lacking, imatinib, sorafenib and pazopanib are agents used in the treatment of DT. Heinrich et al., in one of the first studies on imatinib, reported that 19 patients with progressive disease showed a partial response, and three patients (16%) achieved a three-year PFS with the use of imatinib at 800 mg/day (36). Penel et al.'s study included 40 DT patients with progressive disease, who were treated with imatinib at 400 mg/day. They reported that the one-year PFS rate was 67%, and the two-year PFS rate was 55% (35). Three of the patients in our study received imatinib as a second-line treatment and one patient as a third-line treatment. The median PFS was 23.2 (range 4.30-31.6) months in the former and 8.23 months in the latter.

LIMITATIONS

The limitations of our study are that it is retrospective, lacks heterogeneity and includes a small number of patients and only two data centers.

CONCLUSION

The results of our 15 patients, who were treated with surgery, radiotherapy and systemic treatments, are largely similar to those reported in the literature and, overall, are quite good. Because DTs are very rare, prospective randomized studies are lacking in the literature. Most of the data about this disease come from a few retrospective studies and case reports. Therefore, we think that our patient series will contribute to the literature .

Competing Interests: The authors declare that they have no competing interest.

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Table 1. General features of cases

Patient Number	Age	Gender	Localization	Resection Margin	Adjuvant RT	Recurrence	First-line Treatment	First-line PFS Months	Second-line Treatment	Second-line PFS Months	Third-line Treatment	Third-line PFS Months	Exitus	OS	Follow-up Time
1	34	Female	Abdominal Wall	R2	No	-	Dacarbazine Adriamycin	15.10	Tamoxifen Sulindac	38.0			Yes	71.4	71.4
2	18	Male	Extremity	R1	No	Yes	Tamoxifen Sulindac	89.40	-					-	170.7
3	18	Male	Intra abdominal	R0	No	Yes	Dacarbazine Adriamycin	37.03	Tamoxifen Sulindac	5.33	İmatinib	8.23	Yes	100.83	100.83
4	48	Male	Intra abdominal	R2	No	-	Dacarbazine Adriamycin	25.73	-				Yes	52.60	52.60
5	26	Female	Abdominal Wall	R1	No	Yes	Tamoxifen Sulindac	89.87	-					-	93.23
6	30	Female	Abdominal Wall	R0	No	Yes	Tamoxifen Sulindac	31.47	Imatinib	23.27				-	91.00
7	38	E	Abdominal Wall	R0	No	No	-	-	-					-	14.87
8	42	E	Extremity	R2	Yes	Yes	-	-	-	-	-	-	-	-	16.77
9	45	Female	Abdominal Wall	R0	No	Yes	Tamoxifen Sulindac	22.77	Dacarbazine Adriamycin	7.03			Yes	77.13	77.13
10	28	E	Extremity	R0	No	Yes	Recurrence Surgery RT	-	-	-	-	-	-	-	20.13
11	32	Female	Abdominal Wall	R0	No	Yes	Recurrence Surgery	-	-	-	-	-		-	78.53
12	40	Male	Chest Wall	R1	Yes	Yes	Tamoxifen Sulindac	13.23	Imatinib	31.67				-	44.97
13	45	Female	Intra abdominal	Unresectable	No	-	Methotrexate Vinorelbine	8.63	Imatinib	4.30			Yes	30.60	30.60
14	36	Male	Extremity	R1	Yes	No	-	-	-	-	-	-	-	-	48.77
15	33	Female	Abdominal Wall	R0	No	No	-	-	-	-	-	-	-	-	2.66

REFERENCES

1. Mitchell G., Thomas JM., Harmer CL. Aggressive fibromatosis: Evidence for a stable phase. Sarcoma 1998;2:149-54.
2. Kasper B, Ströbel P, Hohenberger P. Desmoid tumors: Clinical features and treatment options for advanced disease. The Oncologist 2011;16:682-93.
3. Kallam AR, Ramakrishna BV, Roy GK, et al. Desmoid tumours: Our experience of six cases and review of literature. J Clinical & Diagnotic Research 2014;8: NE01-04.
4. Mankin HJ, Hornicek FJ, Springfield DS. Extra-abdominal desmoid tumors: a report of 234 cases. J Surg Oncol 2010;102:380-4.
5. Klemmer S, Pascoe L, DeCosse J. Occurrence of desmoids in patients with familial adenomatous polyposis of the colon. Am J Med Genet 1987;28:385-92.
6. Skubitz KM. Biology and treatment of aggressive fibromatozis or desmoid tumor. Mayo Clin Proc 2017;92:947-64.
7. Fiore M, MacNeill A, Gronchi A, et al..Desmoid-type fibromatosis: Evolving treatment standards. Surg Oncol Clin N Am 2016;25:803-26.
8. Nicolas P, Frederic C, Sebastien S. Adult desmoid tumors: Biology, management and ongoing trials. Current. Opinion in Oncology 2017;29:268-74.
9. Penel N, Coindre JM, Bonvalot S, et al. Management of desmoid tumours: A nationwide survey of labelled reference centre networks in France. Eur J Cancer 2016;58:90-9.
10. Van Broekhoven DL, Verhoef C, Elias SG, et al. Local recurrence after surgery for primary extra-abdominal desmoid-type fibromatosis. Br J Surg 2013;100:1214-9.
11. Sakorafas GH, Nissotakis C, Peros G, et al. Abdominal desmoid tumors. Surgical Oncology 2007;16:131-42.
12. Papagelopoulos PJ, Mavrogenis AF, Mitsiokapa EA, et al. Current trends in the management of extra-abdominal desmoid tumours. World J Surg Oncol 2006;4:21
13. Crago AM, Denton B, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. Ann Surg 2013;258:347-53.
14. Lazar AJF, Hajibashi S, Lev DC, et al Desmoid tumor: From surgical extirpation to molecular dissection. Curr Opin Oncol 2009;21:352-9.
15. Salas S, Dufresne A, Bui B, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: A wait-and-see policy according to tumor presentation. J Clin Oncol 2011;29:3553-8
16. Bonvalot S, Eldweny H, Haddad V, et al. Extraabdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients. Eur J Surg Oncol 2008;34:462-8.
17. Ballo MT, Zagars GK, Pollack A et al. Desmoid tumor: prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. J Clin Oncol 1999;17:158-67.
18. Peng PD, Hyder O, Mavros MN, et al. Management and recurrence patterns of desmoids tumors: a multi-institutional analysis of 211 patients. Ann Surg Oncol 2012;19:4036-42.
19. Bonvalot S, Eldweny H, Haddad V, et al. Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients. Eur J Surg Oncol 2008;34:462-8.
20. Gentile MS, Jacobson A, Wang H, et al. Outcomes in patients with recurrent desmoid tumor managed with surgery alone, combined surgery and radiation therapy, or radiation therapy. International J Radiation Oncology Biology Physics 2016;96: 704-5
21. Bertagnolli MM, Morgan JA, Fletcher CD, et al. Multimodality treatment of mesenteric desmoid tumours. Eur J Cancer 2008;44:2404.
22. Monneur A, Chetaille B, Perrot D, et al. Dramatic and delayed response to Doxorubicin-dacarbazine chemotherapy of a giant desmoid tumor: Case report and literature review. Case Rep Oncol 2013;6:127-33.
23. Skapek SX, Ferguson WS, Granowetter L, et al. Vinblastine and methotrexate for desmoid fibromatosis in children: Results of a pediatric oncology group Phase II Trial. J Clin Oncol 2007;25:501-6.
24. Garbay D, Cesne AL, Penel N, et al. Chemotherapy in patients with desmoid tumors: A study from the French sarcoma group (FSG). Ann Oncol 2012;23:182-6.
25. Palassini E, Frezza AM, Mariani L, et al. Long-term efficacy of methotrexate plus vinblastine/vinorelbine in a large series of patients affected by desmoid-type fibromatosis. Cancer J 2017;23:86-91.
26. Eastley N, McCulloch T, Esler C, et al. Extra-abdominal desmoid fibromatosis: A review of management, current guidance and unanswered questions. Eur J Surg Oncol 2016;42:1071-83.
27. Signoroni S, Frattini M, Negri T, et al. Cyclooxygenase2 and platelet-derived growth factor receptors as potential targets in treating aggressive fibromatosis. Clin Cancer Res 2007;13:5034-40. .
28. Aitken SJ, Presneau N, Kalimuthu S, et al. Next-generation sequencing is highly sensitive for the detection of beta-catenin mutations in desmoid-type fibromatoses. Virchows Archiv :An İnternational J Patology 2015;467:203-10.
29. Misemer BS, Skubitz AP, Manivel JC, et al. Expression of FAP, ADAM12, WISP1, and SOX11 is heterogeneous in aggressive fibromatosis and spatially relates to the histologic features of tumor activity. Cancer Med 2014;3:81-90.
30. Kotiligam D, Lazar AJF, Pollock RE, et al. Desmoid tumor: A disease opportune for molecular insights. Histol Histopathol 2008;23:117-26.
31. Skapek XS, Anderson JR, Hill DA, et al. Safety and efficacy of high-dose tamoxifen and sulindac for desmoid tumor in children: Results of a children's oncology group (COG) phase II study. Pediatric Blood &Cancer 2013;60:1108-12.

32. Brooks MD, Ebbs SR, Colletta AA, et al. Desmoid tumours treated with triphenylethylenes. Eur J Cancer 1992;28A:1014-8.
33. Tsukada K, Church J M , Jagelman D G , et al. Noncytotoxic drug therapy for intra-abdominal desmoid tumor in patients with familial adenomatous polyposis. Dis Colon Rectum 1992;35:29-33.
34. Quast DR, Schneider R, Burdzik E, et al. Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: A single-center long-term observational study in 134 patients. Familial Cancer 2016;15:31-40.
35. Penel N , Cesne AL, Bui BN, et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): An FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. Ann Oncol 2011;22:452-7.