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ARAŞTIRMA / RESEARCH

Clinicalopathological evaluation of soft tissue myxofibrosarcoma

Yumuşak doku mikzofibrosarkomunun klinikopatolojik incelemesi

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Abstract

Purpose: The aim of this study is to evaluate the relationship between the clinical course of these tumors by emphasizing the epidemiological data as well as the pathological features of different myxofibrosarcoma cases.
Materials and Methods: 22 cases of myxofibrosarcoma were included in the single center study. Age, gender, tumor location, size, histopathological features as well as treatment modalities and clinical follow-up of the cases were also evaluated. Additional immunohistochemical studies were applied for the differential diagnosis in pathological evaluation.
Results: The mean age of the patients was 54 years old and there is no sex predilection. The extremities are the most common location. Deep located myxofibrosarcoma were highly aggressive unlike superficial counterparts. The grade given as a result of pathological examination is closely related to the clinical course. Since the mean recurrence period is 16 months, long term follow up is required. Recurrence is present in all metastatic cases. Death from the disease occurred only in those with a higher grade.
Conclusion: Myxofibrosarcomas are rarely seen but diagnostically challenging. Accurate diagnosis is essential to differentiate myxofibrosarcoma from other pleomorphic sarcomas, and to manage the treatment of patients since it may mimic even reactive lesions by histopathologically. Superficial and low grade myxofibrosarcoma of present study showed excellent prognosis and it has been presented as a contribution to the literature that these patients may have a good prognosis with correct diagnosis and treatment.
Keywords:. Myxofibrosarcoma, soft tissue, pathology

Öz

Amaç: Bu çalışmada amaç, farklı mikzofibrosarkom vakalarının epidemiyolojik verileri yanı sıra patolojik özelliklerini vurgulayarak bu tümörlerin klinik gidişi ile ilişkisini değerlendirmektir.
Gereç ve Yöntem: Tek merkezli çalışmaya 22 mikzofibrosarkom olgusu dahil edilmiştir. Olguların yaş, cinsiyet, tümör yerleşimi, çapı, histopatolojik özellikleri yanı sıra tedavi yöntemleri, klinik takibi de araştırılmıştır. Patoloji değerlendirmesinde ayırıcı tanıya yönelik ek immünohistokimyasal çalışmalar yapılmıştır.
Bulgular: Bu seride ortalama yaş 54 olup kadın-erkek oranı eşittir. Ekstremiteler en sık yerleşim yeridir. Yüzeyel yerleşmiş tümörler, derin yerleşim gösterenlere kıyasla belirgin olarak iyi seyretmektedir. Patolojik değerlendirme sonucu verilen grade ile klinik gidiş yakın ilişkilidir. Ortalama rekürrens süresi 16 ay olduğu için olguların uzun dönem takibi gereklidir. Metastaz görülen tüm olgularda öncesinde rekürrens mevcuttur. Hastalıktan ölüm sadece yüksek dereceli olanlarda gerçekleşmiştir.
Sonuç: Sonuçta bu tümörler çok nadir görülmekle birlikte tanıda zorluk yaratması bakımından önem teşkil etmektedir. Histopatolojik olarak reaktif lezyonlarla bile karışabilmesi nedeniyle doğru tanı koymak hasta yönetiminde şarttır. Bu tümör grubunda bizim serimizde yüzeyel olanlar ve derecesi düşük olanlar çok iyi seyirli olup, doğru tanı ve tedavi ile bu hastaların iyi prognozlu da olabileceği literatüre katkı olarak sunulmuştur.

Anahtar kelimeler: Miksofibrosarkom, yumuşak doku, patoloji

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INTRODUCTION

Benign and malignant mesenchymal tumors can represent myxoid areas but some tumors are entirely composed of the myxoid matrix such as myxoma, myxofibrosarcoma, myxoid liposarcoma and myxoid chondrosarcoma. These myxoid rich soft tissue tumors are a heterogenous group of lesions with distinct clinical, morphological, molecular and prognostic features. The myxoid nature obscures the typical defining features of specific neoplasms. Small biopsies comprise problematic in myxoid lesions and pathologists have a doubt for definitive diagnosis, because 30% of sarcomas are misclassified at initial biopsy[1]. Ancillary studies of immunohistochemistry (IHC) or molecular techniques are helpful for further evaluation. The morphological trademarks should be looked for regardless of myxoid areas. Occasionally, any feature can not be helpful to approach a certain diagnosis.

In 1977, Enzinger and Weiss found out a subtype of malignant fibrous histiocytoma which was predominantly composed of myxoid areas showed a better prognosis than storiform or pleomorphic variants[2]. Until 2013 WHO classification, myxofibrosarcoma (MFS) was classified under malignant fibrous histiocytoma just before recent innovation in molecular biology techniques and immunohistochemistry now it is accepted as a separate entity[3]. MFS is a malignant myxoid tumor of extremities seen in the elderly population. The clinical presentation is not pathognomonic and it represents as a painless mass with the predilection for the lower extremities[2]. Unlike other myxoid stroma rich soft tissue neoplasms, MFS is prominently seen in superficial tissues. Diagnosis is based on the exclusion of a variety of myxoid and pleomorphic tumors. Grossly it is composed of a lobulated, firm or myxoid tissue, often infiltrating the adjacent soft tissues. Especially the spread of MFS has a tendency along vascular and fascial planes. Infiltrative nature enables high local recurrence rates and mostly the prognosis depends on complications of recurrences[4].

A gross sampling of the tumor is essential to show myxoid nature in these heterogenous areas of MFS. Histopathologically, MFS exhibit divergent areas ranging from a hypocellular lesion to pleomorphic sarcomas. Myxoid stroma is more prominent in lower grade lesions. Necrosis is a common feature of high grade MFS. By FNCLCC grading system, MFS does not have a specific differentiation score, ranges between grade 1 to grade 3. Grade usually reflects the clinical behavior except for recurrences in low grade MFS, but the risk of metastasis is very low for purely low grade tumors.

Surgery with tumor-free margins and adjuvant radiotherapy is accepted treatment choice. Postoperative inflammation can be a diagnostic problem for local recurrence by imaging methods and can cause delayed diagnosis and poorer outcomes. Cross-check of imaging patterns of prior and recurrent tumors show similar features[5].

The location, clinical features and imaging findings are helpful for distinguishing other neoplasms with myxoid components. The aim of this study is to review the clinical results for the treatment of MFS with surgery and/or radiotherapy in a single institution.

MATERIALS AND METHODS

Ethics Committee of Cukurova University approved this study with the protocol number TTU20153799. All patients gave written informed consent before enrolment into the study upon request to Helsinki Declaration study protocol 2013.

Patient cohort

Twenty-two MFS patients that were diagnosed between 2000-2019 were enrolled into this study. Eligibility criteria included 1) biopsy-confirmed MFS patients, 2) adequate for immunohistochemistry. Exclusion criteria are defined as follows; 1) patients with an inadequate sample to review.

Tumor characteristics

This study was based on a review of MFS in a perspective of WHO classification, 2020 by clinical followup information for survival analysis. The pathological diagnosis depends on this classification; the essential issues are defined as multi nodular architecture, infiltrative margins, myxoid stroma, variable pleomorphic cells, distinctive curvilinear vessels[3]. According to the French National Federation of Cancer Centers (FNCLCC) grading system, tumors of grade I and II were classified as low grade and grade III tumors were classified as high grade.

Immunohistochemistry method and evaluation

Paraffin-embedded blocks were evaluated and selected blocks were stained with variable immunohistochemical antibodies for differential diagnosis. The antibodies such as CD 34 (BioSB, CA, USA, 1:30); MUC 4 (Santa Cruz, CA, USA, 1:50); SMA (Biogenex, USA, 1:80); H-caldesmon (BioSB, CA, USA 1:300); Calponin (BioSB,CA, USA RTU); Desmin (Dako, CA, USA 1:100); S 100 (Dako, CA, USA 1:800); CD 68 (Dako, CA, USA 1:100) were stained by Ventana-Benchmark automated stainer. For each of the antibodies, staining has assessed the presence of tumor cells and for the proportion of positivity of tumor cells. Cytoplasmic staining of S 100, SMA, H-caldesmon, calponin, desmin and membranous MUC 4, CD 34, CD 68 staining are accepted as positive.

Procedure

Biopsy samples were reviewed morphologically by two pathologists (KEE, GG). All slides were reviewed and re-diagnosed according to WHO classification system without discordance. The patients were evaluated as age, gender, location, tumor volume, biopsy technique, surgical margins, treatment protocols, recurrence and survival time. Recurrence is defined as tumor regrowth after complete excision in the same location. Survival is defined as expected lifetime after diagnosis.

Statistical analysis

Statistically student T-test analysis was used to compare the demographic, morphologic features, tumor location and clinical course as well as kappa test to identify the variations between two pathologists by SPSS 19.0.

RESULTS

The patients were diagnosed at an average age of 54,9 years (min: 28 years old, max: 82 years old) with an equal ratio of M: F. Most of the tumors arose in the limbs (86 %). The patients which showed solid sheets of spindled and pleomorphic tumor cells with numerous mitotic figures and necrosis were given a FNCLCC grading system high grade (grade 3) tumors of 72 %. The demographic and clinicopathological data were analyzed in the departments of orthopedic surgery and pathology, and the findings were summarized in the Table 1.

Table 1. Epidemiological, pathological and clinical findings of cases

No	Age	Sex	Location	Tumor vol	Grade	IHC	Follow-up time (Mo)	Status
1	69	M	Upper extremity	NA	Low	CD 34(-), SMA (-), MUC4 (-), S100 (-)	NA	NA
2	57	M	Lower extremity, proximal Deep	890 cm3	High	CD 34(-), SMA (-), Desmin (-), S100 (-)	41	DWD
3	51	M	Lower extremity Superficial	780 cm3	High	CD 34(-), SMA (-), Desmin (-), S100 (-)	74	Metastatic to the lung, DWD
4	82	F	Lower extremity, quadriceps Deep	1300 cm3	High	CD31(-), CD34 (-), SMA (-), Desmin (-), S100 (-)	1	DWD
5	54	M	Upper extremity, Deep	144 cm3	High	CD117 (-), CD34 (-), SMA (-), Desmin (-), S100 (-)	61	Metastatic to the lung, DWD
6	53	M	Dorsum, infraspinatus Deep	3600 cm3	High	S100 focal (+), SMA focal (+), Desmin (-),CD34 (-)	28	Metastatic to the lung, DWD
7	69	M	Upper extremity, proximal Deep	160 cm3	High	S100 focal (+), SMA (-), Desmin (-),CD34 (-)	72	Alive

8	65	M	Dorsum, infraspinatus Deep	NA	Low	CD 34(-) SMA (-), Desmin (-), S100 (-), MUC4 (-)	72	Alive
9	60	F	Lower extremity Superficial	710 cm3	High	CD 34(-) SMA (-), Desmin (-), S100 (-)	68	Alive
10	28	M	Upper extremity, proximal Deep	1836 cm3	High	CD34 (-), EMA focal (+), SMA (-), Desmin (-), S100 (-)	6	Metastatic to the lung, DWD
11	28	F	Upper extremity Superficial	16 cm3	Low	S100 focal (+), SMA focal (+), MUC4 (-), CD34(-)	44	Alive
12	50	F	Lower extremity, proximal, vastus lateralis Deep	318 cm3	High	CD 34(-) SMA (-), Desmin (-), S100 (-)	46	Metastatic to the lung, Alive
13	54	F	Lower extremity Superficial	NA	Low	CD 34(-), SMA (-), Desmin (-), S100 (-), MUC4 (-)	60	Alive
14	56	F	Lower extremity, proximal Deep	NA	Low	CD 34(-), SMA (-), Desmin (-), S100 (-), MUC4 (-)	60	Alive
15	65	M	Lower extremity Superficial	NA	High	CD 34(-) SMA (-), Desmin (-), S100 (-)	60	Alive
16	59	F	Upper extremity, forearm flexor Deep	82 cm3	High	S100 (-), MUC4 (-), SMA (-), Desmin (-), CD34 (-)	25	Alive
17	53	M	Lower extremity, proximal Deep	579 cm3	High	S100 (-), TLE1 (-), SMA (-), Desmin (-)	12	NA
18	50	M	Lower extremity Superficial	1031 cm3	High	S100 (-), SMA (-), CD 34 (-), Desmin (-)	24	DWD
19	62	F	Abdominal, superficial	795 cm3	Low	CD 34(-), B-katenin (-) SMA (-), Desmin (-), S100 (-)	30	Alive
20	64	F	Lower extremity Superficial	NA	High	CD 34(-), SMA (-), Desmin (-), S100 (-)	12	Alive
21	50	F	Lower extremity, proximal, vastus lateralis Deep	73,5 cm3	High	CD34 (+), S100 (-), SMA (-), Desmin (-)	12	Alive
22	29	F	Lower extremity, proximal Deep	4420 cm3	High	SMA (+), S100 focally (+), CD34 (-), Desmin (-)	6	DWD

F, female; M, male; DWD, deceased with disease; NA, not available; SMA, smooth muscle actin; EMA, epithelial membrane antigen; MUC-4, Mucin 4.

Each of the patients except five (only paraffin blocks of consultation cases were evaluated) in this cohort underwent either a wide excision or amputation for definitive diagnosis.

Tumor sizes were between 45-202 mm. Tumor volume ranges from 2 to 4420 cm3, the mean tumor volume was 1045 cm3. High-grade tumors' mean size was 112 mm and mean tumor volume was 1137 cm3. Low-grade tumors' mean volume was 400,5 cm3. High-grade tumors tend to be bigger than low grade MFS cases.

The surgical margins were free in 14 cases. Two specimens showed tumor cells in the edge of surgical margins. These two patients did not have metastatic disease and they are alive.

Five cases that had high-grade tumors received adjuvant chemotherapy and radiotherapy. Among these, three cases have died from disease but two cases were alive.

The reviewing cases reveal a multinodular growth pattern of variable cellularity at low power examination. Tumor cells are spindle or stellate shaped and are deposited in a myxoid matrix. The cells have eosinophilic cytoplasm, indistinct borders; the nuclei are hyperchromatic and pleomorphic. Stromal curvilinear capillaries are prominent (Figure 1).

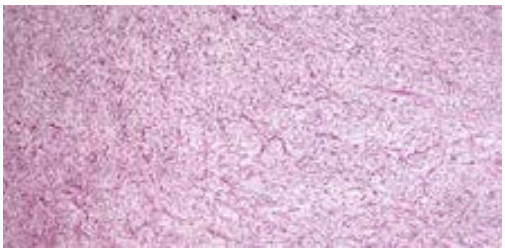

Figure 1. (H&E, X40) Spindle cells with indistinct borders and prominent atypical cells were seen.

Low-grade MFS cases show hypocellular myxoid areas, scant mitotic figures with atypia without necrosis (Figure 2). High-grade cases showed atypical cells with a hyperchromatic nucleus, prominent nucleoli, high cellularity with extensive necrosis with high mitotic count (Figure 3).

To evaluate the survival of patients, clinical follow-up data were used. In this cohort, eight patients are deceased with the disease (DWD); 12 patients are alive and 2 patients have no follow-up information. Four patients who develop distant metastasis are deceased with the disease. There were no correlation between positive surgical margins and DWD, unless all died patients had high grade tumors. Clinical follow-up reveals that three patients that are high-grade were found to have local recurrence at a median of 16 months (range: 4 to 24 months) from the initial diagnosis. All recurrent cases developed distant metastasis to the lung. Among the 22 cases, five patients had distant metastatic disease to lung (22%), and two of five distant metastatic patients had also lymph node metastasis (9%). The patients with low-grade MFS had excellent survival that none of them died from the disease. (data is shown in table 2)

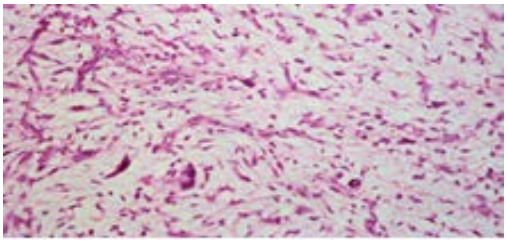

Figure 2. (H&E, X100) Low grade MFS. Hypocellular tumor was composed of bland spindle cells with curvilinear vessels and myxoid background.

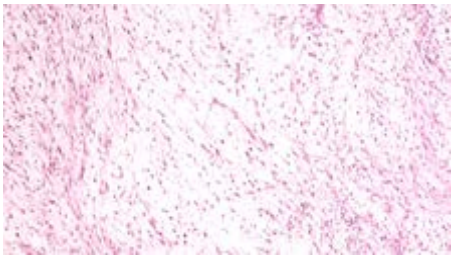

Figure 3. (H&E, X200) High grade MFS. Hypercellular tumor was composed of pleomorphic |spindled cells in a myxoid background. The cells showed frequent mitotic figures.

Table 2. Clinical course of low grade and high grade MFS.

	Tumor volume (mean)	Metastasis (n)	DWD (n)
Low-Grade MFS (n:6)	400,5 cm3	0	0
High-Grade MFS(n:16)	1137 cm3	5	8

MFS, myxofibrosarcoma; DWD, deceased with disease.

DISCUSSION

We evaluated twenty-two MFS with clinical follow-up data as well as pathological features. The low grade MFS patients showed excellent prognosis but superficially located high-grade two patients have died from disease. The mean survival time was 36 months. Distant metastasis was seen in 22 % of all patients. The DWD rate was 36 %. Even high recurrent rates and distant metastases, the overall survival of MFS is better than other soft tissue sarcomas[6,7]. The subtle and nonspecific morphological features cause misdiagnosis, and inconvenient treatment. Our study suggests that the accurate diagnosis, grade and location of MFS may predict clinical outcomes.

Myxoid stroma is produced by neoplastic cells and is not found in normal tissues of adults. The matrix is composed of sulfated and non-sulfated glycosaminoglycans. The water-rich content is responsible for low and high signal intensity on T1 and T2 MRI respectively. In the extremities, less commonly in the trunk, T2 bright and T1 hypo-intense tumor with enhancement on MRI allows a clue of myxoid neoplasm. The imaging features should be supported by the pathological features.

MFS was previously named as malignant fibrous histiocytoma with myxoid features. But now it is a separate entity because of the pathogenesis and behavioral differences from undifferentiated pleomorphic sarcoma[2,8]. It is the most common sarcoma seen in elderly adults[9]. The mean age was 54,9 years and it is compatible with literature, but in our series there were two 28 years old patients. One of these two young patients had high-grade MFS with 202 mm size, distant metastasis and died from the disease after 6 months from initial diagnosis. The other patient had low-grade MFS and she is still alive after 44 months from the diagnosis. One study showed that there is no correlation between age and survival in MFS[10].

MFS of superficial location (36%) exhibits multinodular gelatinous appearance despite deeper located tumors have a tendency of necrosis and becoming larger than superficial counterparts[11]. As reported in the literature, we found that superficial tumors are smaller (mean size: 79,6 mm) than deeper (mean size: 121,5 mm) counterparts. Also the patients, which were DWD, most commonly found to (75%) have deeply located MFS. One study indicated superficial MFS lacks DWD4 but in our series, 2 patients with superficial location died from the disease. These patients have high-grade tumors, one patient has 5 cm (50mm) metastatic disease and another patient has 16,5 cm (165mm) non-metastatic, non-recurrent disease. Superficial MFS tends to have prolonged survival because depth of the lesion is suggested as a prognostic indicator[4].

Rarely MFS in the kidney, brain, head and neck, larynx, sinus piriformis, abdominal wall and hands are reported in the literature[12-18]. One patient had a superficial MFS of low grade in the abdominal wall. Fibromatosis should be ruled out especially for this patient, because low grade MFS and fibromatosis may mimic each other morphologically. B-catenin nuclear positivity is diagnostic for fibromatosis and endothelial cells are more hyper chromatic than tumor cell nuclei in fibromatosis, the opposite should be true in MFS.

The morphology depends on the grade; low-grade MFS is composed of hypocellular tumor of spindle cells that have mild to moderate atypia without necrosis with low mitotic count between 0-6/10 hpf [19,20]. Necrosis and high mitotic counts are compatible with high-grade MFS. Around the vessels the collection of pleomorphic plump, rounded or multinucleated tumor cells may be seen. Pseudolipoblasts which are mucin laden cells mimic true lipoblasts seen in pleomorphic liposarcoma; true lipoblasts are one exclusion criteria for MFS. Myxoid liposarcoma (MLS) may share common morphological features with MFS but the latter has more prominent hyperchromasia and pleomorphism. Also MLS exhibits specific chromosomal alteration of FUS-DDIT3 fusion. The myxoid stroma, dilated cystic like sinusoidal spaces and chicken-wire vessel formation are characteristic features of MLS.

The main differential diagnosis includes other myxoid tumors and the distinction between these tumors can be problematic. Low-grade tumors may be easily mistaken for a benign lesion. It is important that low-grade MFS exhibit tumor cells with coarse chromatin and multilobulated nuclei. Nodular fasciitis, myxoma, spindle cell lipoma, nerve sheath myxoma. Nodular fasciitis exhibit a small lesion with tissue culture fibroblasts, extravasated erythrocytes, inflammation as well as myxoid areas. The typical molecular feature is USP6 gene rearrangements. Cellular/intramuscular myxoma is a benign tumor involving the deep portions of the proximal extremity of 5th decade females and lacks metastasis. It is composed of spindled bland cells embedded in a

myxoid stroma enriched with vessels but the infiltrative areas may occur at the periphery and cause local recurrence. GNAS mutations are helpful in the differential diagnosis[21]. Focal myxoid change is usually seen in solitary fibrous tumor (SFT)[22]. Another problematic differential diagnosis is low-grade fibromyxoid sarcoma (LGFMS). It is commonly seen in young patients including children[23]. LGFMS is composed of bland-looking spindle cells alternating with hypo and hypercellular areas and curvilinear vessels. Despite bland-looking morphology, it has a tendency to late local recurrences and metastases. MUC-4 is a specific and sensitive marker for LGFMS which is negative in MFS; as well as FUS-CREB3L2 fusion is seen in the former.

Surgeons excise most soft tissue sarcomas quite easily except MFS. Surgical margin definition remains unclear whether tumor free standart margins in MFS. Wide excision with a 2 cm margin of the adjacent tissue and removing the biopsy tract is accepted for the optimal treatment choice in soft tissue sarcomas but it is not always possible due to infiltrative pattern and tumor localization in MFS. Another problem especially for superficially located MFS is unplanned excision. The role of radiotherapy to reduce local recurrences of MFS is based on randomized trials[24]. Radiotherapy targets the microscopic remains of tumor tissues. One study showed radiotherapy prevents local recurrence during the first 5 years[4] . In our study three cases received radiotherapy. Two of them who received combined chemotherapy and radiotherapy were still alive after 46 and 25 months unlike the patient who received radiotherapy only has died from the disease within 6 months. It is concluded that chemotherapy may contribute to prolonged life-time.

Local recurrence rates are between 16-57% and it is problematic for surgery because the limb salvage become a problem and the ratio of amputation is between 17-41% for the recurrent tumors[10,25-27]. The risk of recurrence is higher in tumors with positive margins, older age, high-grade tumors[28-30]. Adequate surgical margin is still debated in MFS because even with wide excision, local recurrences may occur. Low-grade and high-grade MFS recurrence rates are 48% and 62%, respectively. Presence of tumor necrosis, tumor size larger than 5 cm and <75% myxoid areas are compatible with higher recurrence rates in low grade MFS[31]. The tumor becomes higher grade in recurrences[32-35]. Mitotic count (≥20/10 hpf) and tumor necrosis ≥10% are highly suggestive of aggressive behavior[29]. The epithelioid variant is another aggressive type of MFS[36,37]. Hypocellular MFS tends to recur rather than metastasis[30].

Metastasis of MFS rates is reported up to 38,2% in different series[38-40]. Girdle located primary tumors have a tendency to metastases rather than limbs, due to the former anatomic location that is rich of vascular and lymphatics[4]. The most common metastatic site is lung, followed by lymph nodes[38-40]. Lymph node metastasis occurs after lung metastasis[41]. In our study, we found lymph node metastasis in two patients (9%) whom had distant metastasis to the lung. MFS which recur within the first year after definitive surgical excision have greater potential to die from disease[19,38]. Our three local recurrent cases have died from the disease within 16,6 months.

Recently Lohberger et al. found two different cell lines in MFS, that MUG-Myx2a cell lines are much higher proliferative and tend to migrate and better chemotherapy response than MUG-Myx2b cell lines[42]. Interestingly, one spontaneous regression of myxofibrosarcoma is reported by Mizuno et al. in the literature[43].

The limitation of this study is the number of cases with follow-up information. As a single center study, unfortunately not all MFS patients preferred to receive further treatment in this center due to personal choices.

In conclusion, MFS is still a challenge for radiologists, pathologists and surgeons. The prognosis is based on tumor biology and invasiveness. MFS consists of variable morphology that mimics benign and malignant myxoid lesions and until now it has not a specific molecular alteration. The pathogenesis of MFS seems to become two different cellular clones which in turn low and high grade areas. Pathologists should be aware of the traps especially in small biopsies thus MFS's differential diagnosis is based on exclusion.

Yazar Katkıları: Çalışma konsepti/Tasarımı: KE, SK, MAD, AG, GG, HSÖ; Veri toplama: KE, SK, MAD, AG; Veri analizi ve yorumlama: KE, SK, MAD, AG, GG, HSÖ; Yazı taslağı: KE, SK, MAD, AG, GG, HSÖ; İçeriğin eleştirel incelenmesi: KE, SK, MAD, AG, GG, HSÖ; Son onay ve sorumluluk: KE, SK, MAD, AG, GG, HSÖ; Teknik ve malzeme desteği: KE, SK, MAD, AG; Süpervizyon: KE, SK, MAD, GG, HSÖ; Fon sağlama (mevcut ise): yok.
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