A case of lung metastasis in myxoinflammatory fibroblastic sarcoma: analytical review of one hundred and thirty eight cases

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Abstract

Purpose Myxoinflammatory fibroblastic sarcoma (MIFS) is a rare soft tissue tumour first identified at the end of the 1990s. This study presents our experience and literature reviews focusing on risk of recurrence.

Methods Rizzoli Orthopaedic Institute database and literature were searched for patients with MIFS observed from 1997 to 2012. Data were analysed in a new database.

Results Five patients underwent surgery at our institute, and 133 cases were retrieved from the literature. Not all clinicopathological data were available: 76/138 were men (55 %), median age was 45 [interquartile range (IQR) 34–56] years, median tumour size was three (IQR two to five) centimetres. Common sites of occurrence were hand (24 %), fingers (23 %) and foot (20 %). Pain was present at diagnosis in 14/82 patients (17 %), with a median duration of seven (IQR three to 12) months. Surgery was performed for a suspected benign tumour in 88 patients (74 %). Resection was incomplete in 45/71 cases (63 %); re-excision was performed in 32/45 (71 %). At a median follow-up of 26 months, 26/118 patients (22 %) developed recurrent disease; median time to recurrence was

15 months (IQR seven to 26). Actuarial relapse-free survival (RFS) at one, three and five years was 93 %, 72 % and 67 %, respectively. At univariate analysis, only symptom duration of six months or less was significantly associated with a worse RFS ($p=0.046$). Metastatic disease to lymph nodes and/or lungs was observed in four patients (3 %).

Conclusions Clinicopathological findings confirm the low-grade nature of MIFS. However, local recurrence occurs, and patients may be affected by aggressive forms with a potential for distant metastases. Follow-up is strongly advised.

Keywords Myxoinflammatory fibroblastic sarcoma · Soft tissue · Lung metastasis · Surgery · Follow-up

Introduction

At the end of the 1990s, Montgomery et al., in a seminal report on 51 patients, first described a rare sarcoma that typically occurs in the distal extremities [1]. Histopathologically, the tumour was characterised by a dense inflammatory infiltrate, myxomatous to hyalinised background stroma in variable proportions, and short spindle- to round-shaped epithelioid cells resembling Reed–Sternberg cells or virocytes were seen. Almost simultaneously, Meis–Kindblom and Kindblom coined the term “acral myxoinflammatory fibroblastic sarcoma” to describe the same entity in 44 patients [2]. This term was subsequently adopted by the World Health Organisation (WHO) in 2002, omitting the adjective acral, as some cases are axial in location [3]. Since then, several case reports and small series on myxoinflammatory fibroblastic sarcoma (MIFS) have been published. However, much of what is currently known about its clinical features and long-term outcome derives mostly from two historical series published in the late 1990s [1, 2]. The aim of this study was to describe

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our experience with MIFS and perform a pooled analysis of published data to provide comprehensive information about clinical features and prognosis of this rare soft tissue tumour.

Methods

Study population

Rizzoli Orthopaedic Institute informed consent, approved by the Ethical Committee, was signed by the five patients who underwent surgery for MIFS from January 1997 to October 2012. The specimens of each patient were independently reviewed by two pathologists (AR and MG) to confirm the original diagnosis. Perioperative and follow-up reports were then retrieved from the institute's database. Data on demographics, medical history, pathology and postoperative follow-up were recorded. At the same time, a MEDLINE search of medical literature published in the last 15 years (January 1997 to October 2012) was performed using the terms “myxoinflammatory fibroblastic sarcoma”, “myxohyaline tumour” and “inflammatory myxoid tumour”. Reference lists of relevant literature were manually cross searched for additional publications. Case series in which data were reported only as generally descriptive or as analytic statistics (i.e. means, medians) were excluded. Similarly, follow-up information that could not be unequivocally linked to a single patient was not considered for analysis. For each article containing patient-specific data, clinical features for each single case were extracted and collected in a dedicated database. Two investigators (RL and NZ) performed the literature search and data extraction and resolved any differences in opinion by consensus. Patients observed at our institution and cases of MIFS retrieved from the literature formed the population of this study (138 patients).

Statistical analysis

Descriptive statistics were calculated, including means $\pm$ standard deviation (SD) and medians plus interquartile ranges (IQR) for continuous variables, and frequencies for categorical variables. Comparisons between variables were performed using Fisher's exact test and the Mann–Whitney *U* test, as appropriate. The following preoperative characteristics were analysed for correlation with marginal excision: age, sex, tumour site (distal extremities vs. other), presence of pain, symptom duration (six months or less versus over six months), tumour size (three or less versus over three centimetres) and surgical treatment (excision vs. amputation). Median follow-up was calculated using the reverse Kaplan–Meier method [4]. Survival curves were drawn with the Kaplan–Meier method and compared by log-rank test. The following variables were examined in univariate analyses of relapse-free survival (RFS): age, sex, tumour site (distal extremities vs. other), presence of

pain, symptom duration (six or less versus over six months), tumour size (three or less versus over three centimetres), surgical treatment (excision vs. amputation), margin status (clear vs. marginal/intralesional) and administration of adjuvant radiotherapy. Two-tailed *p* test of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc, Chicago, IL, USA).

Results

Institution experience

Data of the five patients observed at our institution are summarised in Table 1. Tumours involved distal extremities in two cases. No patient complained of systemic symptoms. At initial evaluation, four patients were thought to have a benign condition, and in one case, a clinical diagnosis of undefined mass was made. No patient had a preoperative biopsy. All cases underwent marginal or intralesional excision at another institution and were referred to us for radical treatment once the histological diagnosis of sarcoma was made. Before re-excision, four patients had locoregional magnetic resonance imaging (MRI) and computed tomography (CT) scan of the chest. One patient (case 2) was staged by locoregional ultrasonography (US) and chest X-ray. In all five cases, a wide tumour bed resection was performed and achieved clear margins. Histological examinations were consistent with residual MIFS. Postoperative radiotherapy was administered in two patients as external beam radiotherapy (EBRT) and combined brachytherapy plus EBRT.

Follow-up information was available for all five cases. Three patients had no recurrence and were alive at 54, 84, and 135 months' follow-up, respectively. One patient (case 3) developed a local recurrence 20 months after initial diagnosis, which was excised with clear margins. The wide soft tissue defect was successfully covered with a free transverse rectus abdominis myocutaneous flap using microsurgery for blood supply restoration. The patient was alive and free from disease at 24 months. In case 5, preoperative CT scan of the chest showed three small, faint opacities in the right lung. Six months after excision of primary tumour, CT scan was repeated showing four nodules in the right lung consistent with metastatic disease (Fig. 1a). After excluding metastases in other sites by positron emission tomography (PET) fused CT scan, the patient was scheduled for thoracic surgery. Intraoperative exploration revealed multiple small nodules under the visceral and parietal pleura associated with pleural effusion. A pulmonary wedge resection was performed for staging purposes, and histological diagnosis of metastatic MIFS was confirmed (Fig. 1b). Currently, the patient is symptom free at 12 months.

Table 1 Clinical features and follow-up data of five myxoinflammatory fibroblastic sarcoma (MIFS) patients treated at Rizzoli Orthopaedic Institute

Case	Sex/age	Tumour location	Tumour size (cm)	Symptoms	Duration of symptoms (months)	Treatment	Follow-up (months)
1	F/51	Left forearm	2.0	Mass	7	E, RE	135, NED
2	M/45	Right hand (dorsum)	1.5	Mass	12	E, RE	84, NED
3	F/24	Left foot (dorsum)	5.0	Mass, pain	3	E, RE, XRT	20, LR (24, NED)
4	M/66	Left upper arm	2.0	Mass	7	E, RE, XRT	54, NED
5	F/54	Right thigh	8.0	Mass	9	E, RE	12, AWD

E excision, *RE* re-excision, *XRT* postoperative radiotherapy, *NED* no evidence of disease, *LR* local recurrence, *AWD* alive with disease

Literature data and pooled analysis of outcomes

Two hundred and thirty-three papers were identified using the described process. Of these, 189 were excluded for the following reasons: not related to MIFS ($n=170$), generic reviews on soft tissue sarcomas ($n=9$), not written in English ($n=4$), relevant reports without patient-specific data ($n=4$), and case reports describing hybrid forms of MIFS ($n=2$). One hundred and thirty-three patients with individual data were retrieved from the remaining 44 articles [1, 5–47]. Clinicopathological features of those 138 patients are reported in Table 2. The tumour occurs approximately equally in men and women, with an overall median age at diagnosis of 45 (IQR 34–56) years. Distal extremities were involved in 94 patients (68 %). In almost half of the cases (47 %), the tumour affected the upper extremities (hands and fingers), which, therefore, represented the most common site. In the lower extremities, MIFS occurred with highest frequency in the dorsum of the foot. Noteworthy, nine patients (7 %) had the tumour located in the trunk or head (Fig. 2); 14 of 82 patients (17 %) complained of pain with no correlation to tumour site ($p=0.133$) or to lesion size ($p=0.154$).

Of the 138 patients, 119 had biopsy or surgery: 16 (13 %) had preoperative biopsy with histopathological diagnosis of MIFS; 88 (74 %) underwent surgery with a clinical diagnosis of benign lesion and 15 (13 %) of suspected neoplasm. In nine

cases, no information was available regarding type of surgery performed. Among the remaining 129 patients, the first surgical treatment was local excision in 118 (91 %) and amputation in 11 (9 %). Mean tumour size ($\pm$ SD) in the latter group was 6.4 cm ($\pm$ 5.5) compared with 3.9 cm ($\pm$ 3.3) in the local excision group, but the difference was not statistically significant ($p=0.065$). Information on margin status was available only for 71 patients. At univariate analysis, only the type of procedure was associated with positive margins (67 % local excision vs. 0 % amputation; $p<0.015$). To achieve radicality, additional surgery was performed in 32 of 45 (71 %) incompletely resected tumours. The rate of positive margins was remarkably lower after revision compared with primary surgery (6 % vs. 63 %; $p<0.001$), whereas the proportion of amputations did not vary significantly (9 % vs. 6 %; $p=1.000$).

Immunohistochemical studies showed that when testing for vimentin was performed, it was strongly positive in all lesions. Tumours often had focal positivity for CD68 (84 %) and CD34 (57 %); immunoreactivity for smooth muscle actin (SMA), S-100 protein, activin receptor-like kinase 1 (ALK-1) and keratin was less common (6–16 %). No cases showed positive staining with CD30, leukocyte common antigen (LCA), desmin, epithelial membrane antigen (EMA), HMB45, and melan-A. Although occasionally tested, immunoreactivity rates for α 1-ACT, α 1-AT, CD95 and CD117 were very high.

Fig. 1 **a** Computed tomography (CT) scan of the chest showing subpleural and parenchymal nodules in the right lung (white arrows). **(b)** Histopathologic low-power view of lung metastasis showing alternating myxoid and hyalinised areas with mixed inflammatory infiltrate

(haematoxylin and eosin, $\times 4$). Inset shows occasional Reed–Stenberg-like cells, with huge, inclusion-like nucleoli (black arrow) within the inflammatory infiltrate (haematoxylin and eosin, $\times 20$)

Table 2 Summary of demographic and clinical characteristics of 138 patients with myxoinflammatory fibroblastic sarcoma (MIFS)

Age, years ^a	
Median (IQR)	45 (34–56)
Mean $\pm$ SD	45 $\pm$ 17
Gender	
Male	76/138 (55 %)
Female	62/138 (45 %)
Size, cm ^b	
Median (IQR)	3.0 (2.0–5.0)
Mean $\pm$ SD	4.0 $\pm$ 3.5
Pain	14/82 (17 %)
Symptom duration, months ^c	
Median (IQR)	7 (3–12)
Mean $\pm$ SD	18 $\pm$ 33
Neoadjuvant EBRT	15/105 (14 %)
Surgical treatment	
Excision	118/129 (91 %)
Amputation	11/129 (9 %)
Marginal/intralesional excision	45/71 (63 %)
Resurgery after incomplete excision	
Excision	30/32 (94 %)
Amputation	2/32 (6 %)
Margin status after resurgery	
Clear	26/32 (81 %)
Marginal/intralesional	2/32 (6 %)
Not reported	4/32 (13 %)
Adjuvant treatment ^d	12/93 (13 %)

All data are number of patients (%) unless otherwise indicated. Percentages are reported with respect to available data

IQR interquartile range, SD standard deviation, EBRT external beam radiotherapy

^a 136 patients

^b 106 patients

^c 43 patients

^d Adjuvant treatment administered as EBRT in eight patients, brachytherapy in two, combined EBRT plus brachytherapy in one and intraoperative radiotherapy in one

One hundred and eighteen patients were available for survival analysis. At a median follow-up of 26 months, overall censoring rate for recurrence was 22 % (26/118 patients). Median time to recurrence was 15 months (IQR 7–26). Thirty-eight per cent of relapses were diagnosed within one year, 88 % within three years, and 92 % within five years. RFS probabilities [$\pm$ standard error of mean (SEM)] were as follows: at one year 93 % ($\pm$ 3); at three years 72 % ($\pm$ 5); at five years 67 % ($\pm$ 7) (Fig. 3). Among the clinicopathological variables, only symptom duration was significantly associated with risk of recurrence at five years (Table 3). First recurrences were local in 25 patients and local with lymph node metastasis in one patient. Of 26 cases with

Fig. 2 Distribution of myxoinflammatory fibroblastic sarcoma (MIFS) in 138 patients

recurrent disease, nine (35 %) developed a second recurrence and four (15 %) developed three or more recurrences. One patient who experienced local recurrence in the calf subsequently developed metastases to inguinal lymph nodes, neck and base of skull; he was alive with disease at 79 months [29]. A second patient developed lung metastasis after local recurrences in the hand and died of disease at 36 months [29]; this was the only case of cancer-related death. Noteworthy, one patient in our series (case 5) at disease onset presented with lung metastases. Distant metastases to lymph nodes and/or lungs occurred in four cases (3 %) during the course of disease.

Fig. 3 Kaplan-Meier estimation of relapse-free survival (RFS) in 118 patients

Table 3 Univariate analysis of risk factors for relapse

Variables	No. patients	5-year RFS ($\pm$ SEM) ^a	P value
Age			0.367
$\leq$ 45 years	62	65 % ($\pm$ 8)	
>45 years	54	74 % ($\pm$ 10)	
Gender			0.730
Male	63	69 % ($\pm$ 9)	
Female	55	69 % ($\pm$ 8)	
Tumour site			0.649
Distal extremities ^b	82	73 % ($\pm$ 6)	
Other	36	45 % ($\pm$ 20)	
Pain			0.324
Yes	11	83 % ($\pm$ 15)	
No	57	67 % ($\pm$ 9)	
Symptoms duration			0.046
$\leq$ 6 months	18	48 % ($\pm$ 17)	
>6 months	15	89 % ($\pm$ 11)	
Tumour size			0.563
$\leq$ 3 cm	52	66 % ($\pm$ 8)	
>3 cm	42	77 % ($\pm$ 9)	
Surgical treatment			0.205
Excision	103	65 % ($\pm$ 7)	
Amputation	9	100 % ($\pm$ 0)	
Margin status ^c			0.333
Clear	45	80 % ($\pm$ 9)	
Marginal/intralesional	12	57 % ($\pm$ 20)	
Adjuvant treatment			0.882
Yes	12	73 % ($\pm$ 13)	
No	74	74 % ($\pm$ 6)	

RFS relapse-free survival, SEM standard error of the mean

^a Unadjusted Kaplan-Meier estimates

^b Hands, fingers, thumbs, feet, toes

^c Final margin

Discussion

MIFS is an extremely rare soft tissue tumour first described as a distinct mesenchymal lesion at the end of the 1990s [1, 2]. To date, approximately 250 cases have been reported in the literature, mostly as single case reports or small cohorts. To our knowledge, our study is the first analytical review on this rare sarcoma.

In accordance with results from the two largest cohorts on MIFS [1, 2], we found that the tumour almost equally affects both genders, with peak appearance in the fourth and fifth decades of life. However, the age range is vast, and approximately 10 % of cases were under 12 or over 75 years old. Regarding tumour location, initial reports overemphasised the predilection for distal extremities, so the term acral myxoinflammatory

fibroblastic sarcoma was coined [2]. Although the adjective acral was deleted from the official nomenclature in 2002 because some cases are located axially [3], its use is still common [19, 20, 26, 28, 29, 32, 34, 36, 39, 45]. Our analysis confirms that distal extremities are involved in the majority of cases, with hands and fingers being the most common sites. However, in almost one third of patients, tumours were not acral in location. Similarly, Jurcic et al. reported three of nine patients with MIFS in a proximal location [8]. Based on these findings, we suggest avoiding the use of the term acral, as it is somewhat misleading.

The tumour typically presents as a solitary, longstanding mass or swelling in the subcutaneous tissue. Although it occasionally reaches considerable size (up to 23 cm), the median tumour diameter at diagnosis is three centimetres [33]. Pain is unusual and complained about by approximately one of five patients. The lack of specific symptoms leads to misdiagnosis, which is still a common problem with potential for inappropriate treatment. Our analysis shows that incomplete tumour resection is significantly more common after primary surgery compared with revision. Histologically, amputation (rather than local excision) proved to be the only predictive factor of clear margins. As the proportion of patients undergoing amputation did not vary significantly, the higher rate of inadequate excision after primary surgery may be explained by physician noncompliance with the principles of surgical oncology as a result of a presumptive benignity. In our study population, 74 % of cases underwent surgery, with a clinical diagnosis of benign disease. The main reason for this is that benign, painless masses in the extremities, such as ganglion cysts and lipomas, are more common than malignant soft tissue tumours. Moreover, the relative simplicity of excisional biopsy encourages surgical exploration, both as a diagnostic and therapeutic measure, without exhaustive preoperative workup. Another explanation for the frequency of positive margins is difficulty in achieving radical excision while preserving functional status, especially when treating large and/or acral MIFS. However, we found no correlation between incomplete excision and tumour location or size.

Grossly, MIFS appears as a poorly circumscribed gray mass, ranging from myxoid to hard in consistency, associated with focally necrotic and/or hemorrhagic areas. Lesion contour varies from lobular, with a pushing margin, to more irregular and infiltrative [29]. The tumour typically arises within the subcutaneous tissue, usually involving the subcutis and deep soft tissues [10, 11, 29]. Histologically, MIFS shows fibrous septa dividing the tumour into lobules, with loose myxoid stroma and focal hyalinised areas associated with capillary proliferation [3, 11]. Neoplastic cells consist of three distinct populations of different morphology: epithelioid cells with mild to moderate nuclear atypia; large polygonal and bizarre cells with prominent vesicular nuclei, often indented or cleaved, inclusion-like nucleoli and abundant eosinophilic cytoplasm (variably described as ganglion-like cells, Reed–Sternberg-like cells and viral inclusion

cells); and bubbly, multivacuolated cells of variable size with intracellular mucins resembling lipoblasts. Mitotic numbers are rare (less than one mitosis per ten high power field). Although to a different degree, a strikingly dense acute and chronic inflammatory infiltrate composed of intermixed lymphocytes, histiocytes, neutrophils and plasma cells, focally obscures tumour cells [1–3, 10, 11, 29]. Concerning the immunohistochemical profile, our results strengthen what is already known. Tumour cells were consistently positive for vimentin, variably positive for CD68 and CD34 and seldom positive for SMA, S-100 protein, ALK-1 and keratin. They lack expression for desmin, EMA, HMB-45, melan-A, and leukocyte markers such as CD45, CD15 and CD30 [1–3, 29]. Given its heterogeneous histological features, MIFS may be mistaken for other mesenchymal neoplasms with myxoid or inflammatory background, such as myxofibrosarcoma (myxoid malignant fibrous histiocytoma), superficial acral fibromyxoma and inflammatory myofibroblastic tumour. Differential diagnosis also includes lesions that arise in distal extremities, such as giant cell tumours of the tendon sheath, as well as Hodgkin's lymphoma and reactive inflammatory processes. However, careful histological scrutiny, appropriate immunohistochemical evaluation and attention to clinical presentation may help guide diagnosis [29, 48].

Surgical excision of MIFS is curative in most cases and represents, therefore, the mainstay in treatment. In selected cases, amputation may be an option when wide resection fails to preserve a functional extremity. Difficulty in achieving local control is unanimously considered the Achilles heel in treatment. In our study population, the crude rate of local recurrence was 22 %, with a five year RFS probability of 67 %. Reported rates of local failure after surgery vary widely in the literature, ranging from 0 % to 67 % [1, 2, 8, 39, 49]. These differences may be due to differences in primary surgical treatment, accuracy of preoperative diagnosis and length of follow-up. Moreover, paucity of study populations in published reports (36 patients at the most) is a factor that notoriously increases variability. Opportunity for improved results may come from the use of complementary treatments, such as radiation therapy. In a report on 17 cases from the Massachusetts General Hospital in the United States, one of the largest recent cohorts, the extensive use of perioperative radiotherapy led to local recurrence in only one case [39].

It is claimed that MIFS should be regarded as a low-grade sarcoma, as, unlike local relapse, occurrence of distant metastases is unusual and the proliferative index rather low. Consistent with this paradigm, we found that metastatic spread to lymph nodes and/or lungs occurred in 3 % of cases during the course of disease. Apart from the four patients in our study, two other cases of metastases—one to inguinal lymph nodes and one to the lung—have been reported [2]. Furthermore, five year RFS at a median follow-up of 26 months was lower in the group of patients with positive margins compared with those who underwent radical excision, but the difference was not statistically significant. This finding could be due to the fact that

differences in rates of clinically detectable recurrence do not stand out in the early postoperative period as a consequence of the low proliferative index. However, caution is warranted when considering MIFS a low-grade sarcoma because in some cases, the tumour behaves aggressively. Recurrences may be multiple and locally destructive. This occurred in 15 % of patients who in our study population experienced recurrent disease. Hassanein et al. reported a case that had progressive disease with metastases to the neck and base of skull after local relapse [29]. The same authors also reported a second case that developed three local recurrences followed by distant metastasis to the lung and died of disease three years after diagnosis [29]. To our knowledge, the latter is the only MIFS-related death. Furthermore, one of our five patients presented with unresectable pulmonary metastases associated with pleural effusion at diagnosis, a typical pattern of aggressive sarcomas. This case is unique because no other case of histologically confirmed synchronous pulmonary metastases from MIFS is reported in the literature. To summarise, these findings support the contention that MIFSs are not all low-grade neoplasms.

Postoperative data allow us to consider two specific issues regarding follow-up: Firstly, postoperative surveillance is advisable, as at least one in five patients requires re-excision for recurrence, which in most cases proves effective. Secondly, radiological examination of the chest should be included in the follow-up programme to detect distant metastases, especially when local failure occurs during postoperative surveillance.

The major limitation of this study is that the patient population did not comprise consecutive cases from a single centre. This implies an underlying heterogeneity that must be kept in mind when interpreting results. However, information about rare diseases is difficult to summarise in a useful form for clinical practice. To this end, analysis of patient-specific data extracted from each report could be valuable. Moreover, the method used in this study is the only one that allows inferential statistics and, of more importance, an estimation of events.

In conclusion, MIFS is a rare soft tissue sarcoma that affects distal extremities less frequently than was classically believed. It is usually discovered incidentally after surgical removal of a presumed benign lesion, which leads to a high rate of incomplete excisions. It is important for surgeons to be aware of MIFS and be prepared to extend resection when exploring a mass in the extremities. Inclusion of MIFS in the category of low-grade sarcomas appears justified by clinical and biological findings. However, it should be kept in mind that some MIFSs display aggressive behaviour. Whether these cases represent an evolution in high-grade sarcoma or a native form of high-grade MIFS remains unknown.

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Conflict of interest None

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