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Case report

Myxoinflammatory fibroblastic sarcoma

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Introduction

Acral myxoinflammatory fibroblastic sarcoma (MIFS) was first described in 1998 as a new entity in three independent reports by pathologists, Meis-Kindblom and Kindblom,[1] Michal,[2] and Montgomery et al.[3] It occurs primarily in adults, with a peak incidence in the fourth and fifth decades of life, and presents as a painless firm mass of the distal extremities, predominantly the hands and feet. Recently, proximally located MIFS has also been reported, and some authors have suggested dropping the adjective "acral" from the name of the tumor because of its possibly misleading nature.[4] Histologically, MIFS is a poorly circumscribed and typically multinodular tumor. The most striking feature is inflammatory infiltration associated with a prominent myxoid matrix in variable proportions and the presence of bizarre virocyte or Reed-Sternberg-like cells and multivacuolated cells simulating lipoblasts.[1–3] Surgical excision with a wide margin is considered the treatment of choice, as the tumor shows a high rate of local recurrence. Meis-Kindblom and Kindblom[1] reported a 67% local recurrence rate within a median follow-up period of 5 years. However, the tumor is frequently difficult to diagnose correctly at the time of initial presentation because of its apparently benign nature, being a slow-growing, small and painless mass in the distal extremity. As a result, there is a tendency for the tumor to be treated inadequately by referring physicians. Surgeons need to be mindful of MIFS, its nature, and the appropriate treatment necessary for this unique tumor.

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Case reports

Five patients with MIFS treated at our institution between 2000 and 2006 were retrospectively reviewed. Complete clinical and follow-up information was obtained in all cases. All histopathological specimens were examined by an experienced pathologist to confirm the diagnosis, and were classified according to the current WHO criteria.[5] We obtained informed consents about publication from all the patients.

Clinical data for the five patients are summarized in Table 1. The patients comprised two males and three females, with a mean age of 47 years (range, 18–83 years). Four patients presented with a painless firm mass and one with a painful mass. The mean symptom duration was 6 months (range, 2–18 months). All the tumors were located in subcutaneous tissue, and the average size was 3 cm (range, 1–5 cm). The primary locations were distal (acral) extremities in three (first web space of the hand, volar aspect of the thumb, and dorsal aspect of the foot), and proximal extremities in two.

Histologically, the tumors showed a vaguely multinodular growth pattern. Myxoid areas were present in various proportions (Fig. 1A). Inflammatory cells, including lymphocytes (Fig. 1B), neutrophilic granulocytes, eosinophils, and plasma cells, were scattered in variable proportions. Neoplastic cells included spindle and epithelioid cells with mild to moderate nuclear atypia, large polygonal and bizarre ganglion-like cells, Reed-Sternberg-like cells with huge inclusion-like nucleoli (Fig. 1C), and multivacuolated lipoblast-like cells. Some epithelioid cells had vesicular nuclei and enlarged eosinophilic nucleoli (Fig. 1D). Occasionally, large mummified cells and necrosis were seen. Multinucleated giant cells, foam cells, and macrophages with foci of hemosiderin deposition were focally seen. The histopathological features in each case are outlined below.

Table 1. Clinical data of patients with myxoinflammatory fibroblastic sarcoma

Case no.	Sex/Age (years)	Location	Symptom	Size (cm)	Treatment in our hospital	Former diagnosis	Follow-up Recurrence/ Metastasis
1	M/61	R. thumb/volar aspect	Mass, pain	1	Additional WE with wrap-around flap	Epithelioid angiosarcoma	55 Months –/–
2	F/32	L. foot/dorsal aspect	Mass	2.5	Additional WE with inguinal free flap	Low-grade malignant tumor	74 Months –/–
3	F/29	R. thigh	Mass	1	Additional WE	MIFS	21 Months –/–
4	F/83	L. thigh	Mass	5	Primary WE with skin graft	None	6 Months –/–
5	M/18	R. hand/first web	Mass	2.5	Additional WE with local flap and skin graft	High-grade pleomorphic sarcoma	7 Months –/–

WE, Wide excision

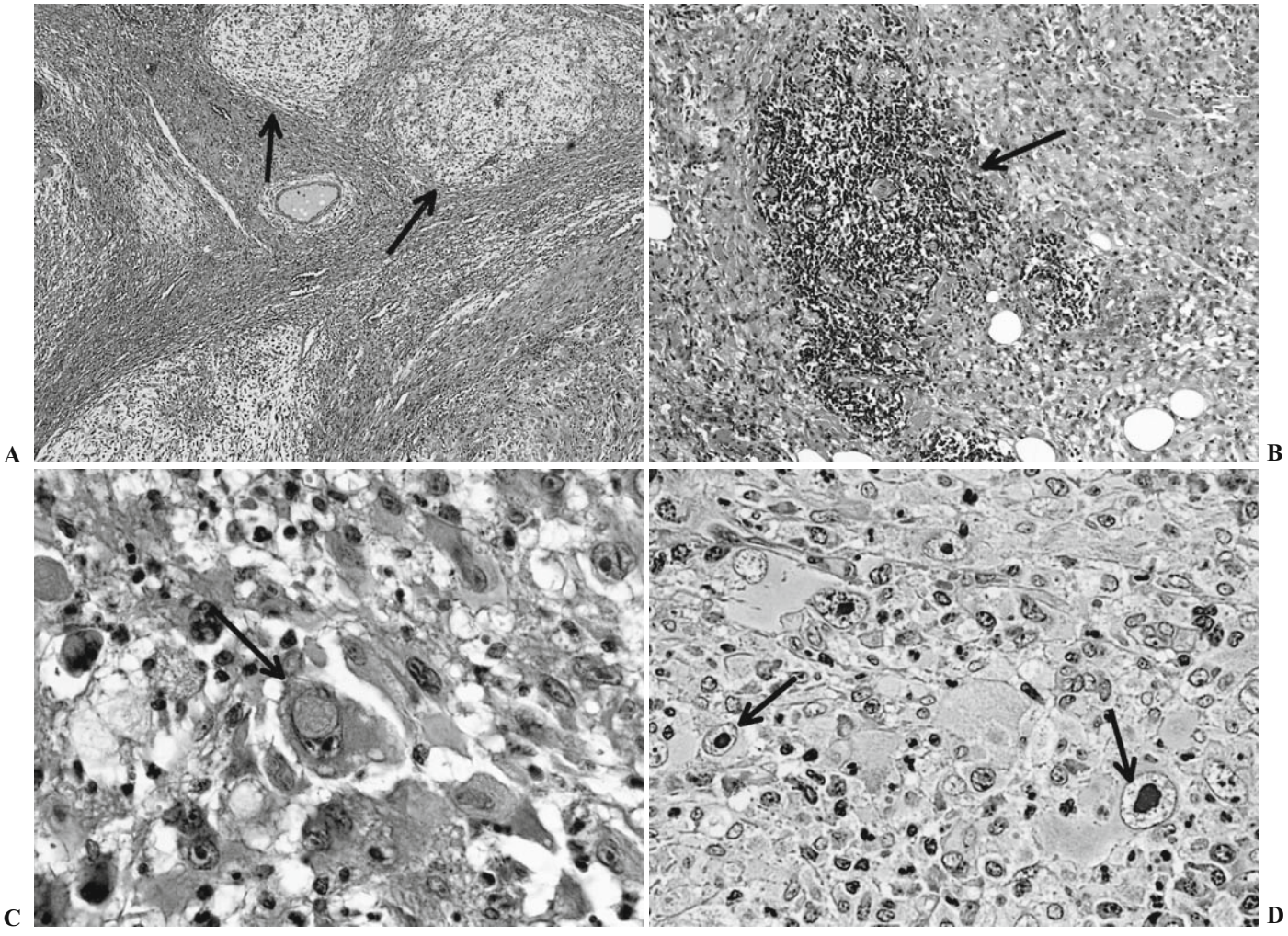

Fig. 1A–D. Histopathological features. **A** Nodular myxoid zone (*black arrows*) demarcated by tumor cells admixed with inflammatory cells. **B** Inflammatory infiltration by a cluster of lymphocytes (*black arrow*). **C** Bizarre tumor cell with huge inclusion-like nucleoli (*black arrow*). **D** Ganglion-like cells (*black arrows*) with eosinophilic nucleoli surrounded by eosinophils and plasma cells. **A** H&E, × 40; **B** H&E, × 100; **C** H&E, × 400; **D** H&E, × 200

Case 1

Tumor cells proliferated in subcutaneous tissue involving tendon sheath. The specimen showed myxoid stroma adjacent to inflammatory infiltration on low magnification. Spindle and polygonal cells were arranged in a sheet-like pattern with Reed-Sternberg-like cells. Necrotic areas and multinucleated giant cells were focally seen.

Case 2

On low magnification, the specimen showed epithelioid cells arranged in a nodular pattern with myxoid stroma and inflammatory infiltration (Fig. 1B). On high magnification, bizarre Reed-Sternberg-like cells with huge inclusion-like nucleoli were scattered.

Case 3

The specimen showed diffusely infiltrated inflammatory cells, most of which were eosinophils and plasma cells. Large ovoid epithelioid cells with vesicular nuclei and enlarged eosinophilic nucleoli resembling ganglion cells were scattered (Fig. 1D).

Case 4

On low magnification the tumor was composed of two areas; a proliferation of large polygonal Reed-Sternberg like cells with myxoid stroma, and a dense fascicular proliferation of spindle and polygonal cells (Fig. 1A). Inflammatory infiltration was scattered and a necrotic area was focally observed.

Case 5

The specimen showed a well-circumscribed tumor with a myxoid area. Spindle and polygonal tumor cells with moderate atypia were seen. Multinucleated giant cells, foam cells, macrophages, and Reed-Sternberg-like cells were focally scattered (Fig. 1C).

Immunohistochemically, vimentin and CD68 were positive in all cases, whereas desmin, S-100, and EMA were negative. Alpha-smooth muscle actin and CD34 were positive in only one case each.

Magnetic resonance (MR) images were performed preoperatively in only two patients (cases 2 and 5). Both tumors showed subcutaneous nodular and poorly circumscribed masses. MR images showed lower intensity than skeletal muscle on T1-weighted images, and usually heterogeneous intermediate-to-high signal intensity on T2-weighted images (Fig. 2A–D). In case 2, the tumor was highly enhanced heterogeneously after injection of gadolinium DTPA (Fig. 2E).

Only one patient (case 4) was suspected to have a malignant tumor at the time of initial presentation, as it was relatively large (5 cm). The other four patients were initially misdiagnosed as having benign tumors, and were treated by marginal or intralesional excision by the referring physicians. The initial pathological diagnoses in these four patients at the referring hospitals were MIFS, high-grade pleomorphic sarcoma, low-grade malignant tumor, and epithelioid angiosarcoma. Local recurrence was observed in case 2, 24 months after the initial inadequate excision.

Wide excision was performed in all five patients at our institution: additional wide excision in four and primary wide excision in one. Soft tissue reconstruction for skin coverage was necessary in the three cases located in the distal extremities. A vascularized free flap was required in two cases (an inguinal free flap and a wrap-around flap). Free skin grafting was performed in two cases. At the time of the last follow up, limb salvage had been achieved in all patients and no definite functional loss was observed. No further local recurrence or distant metastasis was observed after wide excision.

Discussion

MIFS was first described in 1998, as a relatively rare, slow-growing, and low-grade soft tissue sarcoma, in three independent reports by Meis-Kindblom and Kindblom,[1] Michal,[2] and Montgomery et al. [3] We were able to retrieve 133 cases of MIFS through a Medline search (Table 2).[1–4,6–11]

Most of the patients with MIFS had painless small masses; however, Meis-Kindblom and Kindblom[1] reported that pain and restricted mobility were occasionally observed and were more frequently observed with local recurrences. In our series, one patient had a painful mass (case 1).

The tumor occurs typically in the distal extremities, predominantly the hands and feet, although the wrists, forearms, ankles, and legs may also be affected. Proximal (nonacral) MIFS accounted for only 6 (4.5%) of the 133 cases.[4,-8] Jurčić et al.[4] suggested dropping the adjective "acral" from the name of the tumor because of the presence of proximal cases and its possibly misleading nature. Recently this tumor has usually been called myxoinflammatory fibroblastic sarcoma as a synonym of acral MIFS. Most soft tissue tumors of the distal extremities are small and benign, such as ganglion cyst and tendon sheath giant cell tumor. Sarcomas rarely develop in the distal extremities, with the exception of epithelioid sarcoma and clear cell sarcoma. These background factors make it difficult to diagnose MIFS at initial presentation. Although MRI findings specific to MIFS have not been reported, Tateishi et al.[11] recently

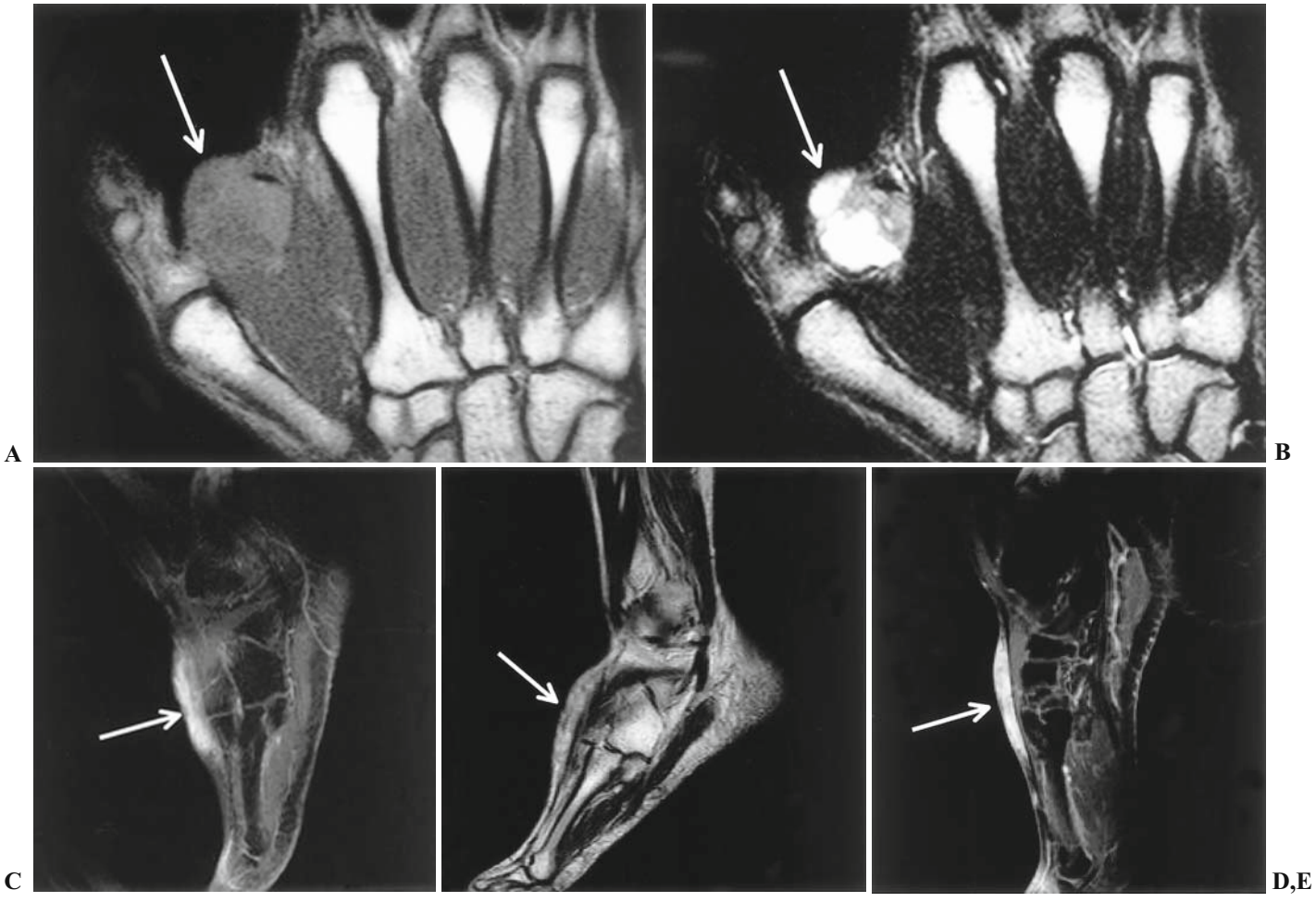

Fig. 2A–E. Magnetic resonance imaging (MRI) findings **A, B** Coronal T1 and T2-weighted MR images show subcutaneous mass in the first web space (*white arrows*; case 5). **C, D, E** Sagittal contrast-enhanced fat-saturated T1-weighted, T2-weighted, and gadolinium enhanced MR images show recurrent subcutaneous tumor in dorsal aspect of the foot (*white arrows*; case 2)

Table 2. Literature review

Authors	No. of cases	Sex Male/ Female	Average age (years)	Location (distal/proximal)	Average size (cm)	Recurrence/ Follow-up cases	Metastasis/Location
Meis-Kindblom and Kindblom [1]	44	22/22	53	44/0	3	24/36	Two, lung and inguinal lymph node
Montgomery et al.[3]	51	27/24	40	39/1	3.4	6/27	None
Michal[2]	5	2/3	46	5/0	2	0/5	None
Jurčić et al.[4]	9	6/3	45	7/2	6.5	1/4	None
Ebhardt et al.[6]	6	4/2	43	5/1	2.4	2/5	None
Lang et al.[7]	5	3/2	40	4/1	2	0/5	None
McFarlane et al.[8]	1	0/1	23	0/1	2	0/1	None
Sakaki et al.[10]	5	4/1	38	5/0	3.7	2/5	One, regional lymph node
Pohar-Marinšek et al.[9]	3	2/1	48	3/0	3.5	1/3	One, adjacent finger
Tateishi et al.[11]	4	3/1	37	4/0	2.4	2/4	None
Our series	5	2/3	45	3/2	3	0/5	None

observed that heterogeneous enhancement on contrast-enhanced MR images corresponded to myxoid areas of the tumor. Lang et al.[7] reported that a tumor showing heterogeneous hyperintensity on T2-weighted MR images with focal hypointense areas might be misdiagnosed as tendon sheath giant cell tumor.

The pathological features in our series of MIFS were similar to those reported previously.[1,2–4,7,9] Significant inflammatory infiltration, various proportions of myxoid areas, and various atypical cells including epithelioid and spindle cells, bizarre ganglion-like cells, Reed-Sternberg-like cells, and multivacuolated lipoblast-like cells were observed. In our series, vimentin and CD68 were positive and desmin, S-100, and EMA were negative in all cases. Immunohistochemical findings in our five cases were consistent with those of the previously reported series, with the exception of positivity for CD34 in one case.[1,2] Meis-Kindblom and Kindblom[1] reported that neoplastic progression was a feature of MIFS cases showing local recurrence, and that recurrent tumors showed an increased number of atypical cells in comparison with the primary tumors. However, the recurrent case in the present series showed no significant increase of atypical cells or mitotic rate.

The differential diagnosis of MIFS based on pathological features covers a broad and varied range of entities depending on whether inflammatory, myxoid, or bizarre atypical components predominate.[1–3,7] A predominance of inflammatory components may suggest tenosynovitis, proliferative or nodular fasciitis, pigmented villonodular synovitis, or tendon sheath giant cell tumor. The presence of myxoid components may lead to confusion with ganglion cyst, myxoid liposarcoma, myxoid chondrosarcoma, or myxofibrosarcoma. On the other hand, the presence of bizarre atypical components may lead to confusion with inflammatory myofibroblastic tumor, inflammatory fibrosarcoma, epithelioid sarcoma, or myxofibrosarcoma. However, the inflammatory lesions observed in tenosynovitis, proliferative or nodular fasciitis, pigmented villonodular synovitis, or tendon sheath giant cell tumor were distinguished from MIFS by the presence of atypical spindle to epithelioid cells.[1–3,10,12] Though myxofibrosarcoma has been reported to be difficult to differentiate from MIFS, a focal area of a storiform and pleomorphic pattern was not observed in MIFS, but was usually seen in myxofibrosarcoma.[1–3,12] In addition, Sakaki et al.[10] have reported that the tumor site is important for distinguishing MIFS from other myxoid tumors, such as myxofibrosarcoma, inflammatory myofibroblastic tumor, or inflammatory fibrosarcoma, all of which occur more proximally than MIFS. Some authors have found clonal chromosomal aberrations in MIFS, such as reciprocal translocation (1;10)(p22;q24) and loss of chromosomes 3 and 13, or supernumerary ring chromosomes composed of chromosome 3 segments.[12,13] These findings support the contention that MIFS is a discrete neoplastic entity, and they can be used to differentiate it from other tumors.

MIFS has been reported to show a high rate of local recurrence after surgical excision (22%–67%), and 38 of the 95 patients who were followed up developed local recurrence (Table 2).[1–4,6,9–11] One of our present cases was a recurrent tumor that was treated successfully by wide re-excision. As MIFS occurs predominantly at superficial sites in distal extremities such as the hand and foot, care should be taken to ensure adequate wide excision, followed by functional reconstruction with viable soft tissue. All of the patients in our current series who have undergone soft tissue reconstruction have achieved good functional outcome without local recurrences. To perform limb salvage, unlike ray amputation, the use of a free vascularized or local fasciocutaneous flap is a valid option for the treatment of MIFS, especially at acral sites.

There have been only four reported cases of metastatic MIFS (lymph nodes in two cases, and lung and adjacent finger one case each; Table 2). In order to screen for recurrence and metastasis, Lang et al.[7] recommended periodical evaluations every 4 months for the first 2 years, and every 6 months thereafter for up to 5 years, as is the case for other low-grade sarcomas.

In conclusion, MIFS is a rare low-grade superficial sarcoma that affects not only the distal extremities but also proximal sites such as the thigh. We should avoid unnecessary amputation for such low-grade sarcomas. To achieve a good oncological and functional outcome, performing wide excision with the use of soft tissue reconstruction, such as a free vascularized or local fasciocutaneous flap, is a valid option for local treatment. It is important for surgeons to be aware of MIFS and to include it in clinical and histological differential diagnoses.

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