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Myxoid liposarcoma of the foot: a study of 8 cases

Elise M Bekers [a,*,1], Wangzhao Song [b,1], Albert JH Suurmeijer [b], Johannes J Bonenkamp [c], Ingrid C van der Geest [d], Petra M Braam [e], Marieke JM Ploegmakers [f], Ingrid ME Desar [g], Bastiaan BJ Tops [a], Joost M van Gorp [h], David H Creytens [i], Thomas Mentzel [j], Uta Flucke [a]

[a] Department of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[c] Department of Surgical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[d] Department of Orthopedics, Radboud University Medical Center, Nijmegen, the Netherlands
[e] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[f] Department of Radiology, Radboud University Medical Center, Nijmegen, the Netherlands
[g] Department of Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[h] Department of Pathology, Diakonessenhuis Utrecht, the Netherlands
[i] Department of Pathology, Ghent University Hospital, Ghent, Belgium
[j] Dermatopathology Bodensee, Friedrichshafen, Germany

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ABSTRACT

Introduction: Myxoid liposarcoma is the only translocation-associated liposarcoma subtype. It classically originates in the deep soft tissues of the thigh. At distal sites of the extremities, this tumor is exceedingly rare. We present a series of 8 cases occurring in the foot/ankle.
Results: Two female and 6 male patients, aged between 32 and 77 years (mean, 54.3 years), were identified. Tumor size ranged from 1.1 to 10 cm (mean, 6.8 cm). Two lesions eroded bone. All tumors were treated by excision and 7 by (neo)adjuvant radiotherapy. R0 status was reached in 2 cases with 1 case followed by metastasis in the groin. All other cases were documented with R1 (n = 2) or R2 (n = 4) resection status. In 1 patient, the follow-up status was unknown. All other patients were alive 15-135 (mean, 55.8) months after initial diagnosis.
We conclude that myxoid liposarcoma at acral sites are exceedingly rare, and in this series, prognosis was good irrespective of resection status. Clinicians and pathologists have to be aware because this sarcoma type shows a peculiar clinical behavior with high radio- and chemosensitivity and metastatic spread to extrapulmonary sites.

1. Introduction

Myxoid liposarcoma (MLS) is the only translocation-associated liposarcoma subtype recapitulating more or less normal lipogenesis [1-3]. The specific fusion genes *FUS-DDIT3* and, more rarely, *EWSR1-DDTI3* are the result of the t(12;16)(q13;p11) and t(12;22)(q13;q12), respectively [3-5].

Myxoid liposarcoma is the most common liposarcoma arising in children, adolescents, and young adults [6-9]. It comprises up to 35% of all liposarcomas and has, in one-third of cases, the tendency to metastasize to other soft tissue sites including mediastinum and retroperitoneum, and also to bone, lung, and liver with a consecutive fatal outcome. The classical localization (two-thirds of the cases) is the deep soft tissues of the thigh [3,6,10]. Cases of the retroperitoneum are almost exclusively metastases with some exceptions [11-13]. At distal sites of the extremities, this tumor is exceedingly rare [6,14-18], and the first case was documented by Booker in 1965 [15]. We here present a series of 8 cases occurring in the foot/ankle.

2. Material and methods

2.1. Patient data

The cases were collected retrospectively from the authors' (referral) files. The study was performed in accordance with the Code of Conduct of the Federation of Medical Scientific Societies in the Netherlands and Germany.

In each case, 4-mm-thick sections of formalin-fixed, paraffin-embedded (FFPE) material were stained with hematotoxylin and eosin. The histological diagnoses were revised (UF, EB) and classified according to the 2013 WHO criteria. From each case, 1 representative paraffin tissue block (4 biopsies and 4 resection specimens) containing the largest area and highest tumor percentage of viable tumor was selected for fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) analysis.

* Corresponding author.
E-mail address: elise_bekers@hotmail.com (E.M. Bekers).

[1] Contributed equally

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2.2. Fluorescence in situ hybridization

Four-micrometer paraffin sections of selected tissue blocks were treated and made accessible to the DNA probes as described earlier in ten Heuvel et al [19]. The used probes were as follows: a telomeric 120-kilobase (kb) probe labeled with Spectrum Orange and a centromeric 334-kb probe labeled with Spectrum Green for *EWSR1* and a telomeric 500-kb probe labeled with Spectrum Orange and a centromeric 270-kb probe labeled with Spectrum Green for *FUS*.

Slides were visually evaluated using a Leica DMR fluorescence microscope equipped with appropriate filters for 4,6-diamidino-2-phenylindole, Spectrum Orange, and Spectrum Green. Tumors (MLS) scored positive for *FUS* and *EWSR1* translocations when several areas contained at least 31% of tumor cell nuclei for *EWSR1* and 13% for *FUS*, and had clearly split orange and green signals (separated by at least 3 signal diameters from an oppositely colored signal).

2.3. Reverse transcriptase polymerase chain reaction

RNA was extracted from FFPE tissues using RNA-Bee-RNA isolation reagent (Bio-Connect BV, Huissen, the Netherlands) according to standard procedures. RNA quantity and quality were determined by NanoDrop measurement (Fisher Scientific, Landsmeer, the Netherlands), and subsequently, cDNA synthesis was performed using Superscript II (Invitrogen Life Technologies Europe, Bleiswijk, the Netherlands) and random hexamers (Promega Nederland, Leiden, the Netherlands).

The cDNA was tested by the RT-PCR for the *HMBS* (hydroxymethylbilase synthase) housekeeping gene using the following primers: forw150 5′-TGCCAGAGAAGAGTGTGGTG-3′, rev150 5′-ATGAT GGCACTGAACTCCTG-3′, forw250 5′-CTGGTAACGGCAATGCGGCT-3′, rev250 5′-TTCTTCTCCAGGGCATGTTC-3′.

For detection of the *EWSR1-DDIT3* fusion, 5′-TCCTACAGCCA AGCTCCAAGTC-3′ forward primer and 5′-GACTCAGCTGCCATCTCTGC-3′ reverse primer were used. For the *FUS-DDIT3* fusion, 5′-GACAGCA GAACCAGTACAACAGCAG-3′ and 5′-CCGTGGTGGCTTCAATAAATTTG-3′ forward primers and 5′-GCTTTCAGGTGTGGTGATGTATGAAG-3′ and 5′-GACTCAGCTGCCATCTCTGC-3′ reverse primers were used. The PCR products were analyzed by agarose gel electrophoresis and Sanger sequencing.

3. Results

3.1. Patient characteristics

Patient characteristics are presented in Table 1. In brief, 8 patients were included of which 2 were women and 6 were men with an age range of 32 to 77 years (mean, 54.3 years; median, 57.5 years). Tumor size ranged from 1.1 to 10 cm (mean, 6.8 cm; median, 6.5 cm). In 4 patients, the tumor was localized between metatarsal 1 and 2; in 1 patient (case 2), it was between metatarsal 2 and 5; and in 2 patients (cases 6 and 8), it was distal in the ankle with extension on the dorsum of the foot. In 1 patient, the specific location, apart from being located in the foot, was unknown. Two lesions (cases 3 and 5) eroded bone with a pathological fracture as clinical presentation in case 3. All lesions were treated by excision/resection, and 7 patients received (neo)adjuvant radiotherapy. R0 status was reached in 2 cases, followed by a metastasis in the groin 7 months later in case 5. All other cases were documented with R1 ($n = 2$) or R2 ($n = 4$) resections without recurrences or metastases. Seven patients were alive after initial diagnosis with follow-up range from 15 to 135 months (mean, 55.8; median, 41.5 months). For patient 8, no follow-up information was available.

3.2. Radiology

Magnetic resonance imaging (MRI), exemplarily described in case 5, showed a well-defined intermetatarsal soft tissue mass with cortical destruction of the adjoining metatarsal bone and involvement of one of the neurovascular bundles (Fig. 1). This heterogeneous mass contained myxoid areas, fatty tissue (less than 25%), and necrotic components. Imaging after contrast agent showed a peripheral nodular enhancement. Six months after radiotherapy, there were an increase in size, bone involvement, and heterogeneous enhancement on MRI with central necrosis. Nine months after radiotherapy and total resection, a lesion in the right groin was found with ultrasonography. This lesion showed a lipomatous aspect, suspicious for metastatic disease.

3.3. Histology

Most cases showed a typical histology of MLS with a nodular growth pattern of relatively low cellularity with enhancement of cells at the periphery of the nodules. There was a proliferation of uniform bland, round to oval primitive cells intermingled with a variable amount of lipoblasts of different stages in an abundant myxoid stroma (Fig. 2). In case 1, an additional nested pattern of primitive cells was seen, and case 4 showed areas of extensive maturation and slightly pleomorphic nuclei (Fig. 3). A delicate plexiform ("chicken-wire") capillary vasculature was present throughout the tumors. Two cases had mainly a hypercellular morphology with more large round cells with increased nuclear-cytoplasmic ratio, distinct nucleoli, and a little amount of intervening myxoid stroma (Fig. 4). In 2 of the 5 neoadjuvant-treated cases, prominent necrosis and/or hyalinization were found with only minimal viable tumor as a result of radiotherapy. The remaining 3 tumors were mainly vital. The groin metastasis of case 5 presented with a prominent round cell pattern. Percentages of the round cell component are shown in Table 2.

Table 1
Clinical data

Case	Age (y)/sex	Tumor size (cm)	Site	Treatment	Rec/met (mo)	Follow-up (mo)
1	65/M	10	Foot	TNF perfusion,R2	No	NED (135)
2	77/M	7	Foot	R1, adjuv RT	No	NED (94)
3	60/M	3.5	Foot	R1, adjuv RT	No	NED (15)
4	39/M	1.1	Foot	Neoadjuv RT, R1	No	NED (85)
5	55/M	4.5	Foot	Neoadjuv RT, R0	Groin (7)	NED (15)
6	32/M	6	Foot/ankle	Neoadjuv RT, R2	No	NED (58)
7	34/F	4	Foot	Neoadjuv RT, R0	No	NED (19)
8	72/F	6.5	Foot/ankle	R0	NA	NA

F, female; M, male; Rec/met, recurrence/metastases; TNF, tumor necrosis factor; R, resection status; Adjuv, adjuvant; Neoadjuv, neoadjuvant; RT, radiotherapy; NED, no evidence of disease; NA, not available.