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Metachronous Bilateral Extremity Soft Tissue Sarcomas

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Case series
Patient: Male, 44 • Male, 58
Final Diagnosis: Soft tissue sarcomas
Symptoms: Discomfort • swelling
Medication: —
Clinical Procedure: Image guided biopsy • metastatic work up • neoadjuvant radiotherapy • radical resection
Specialty: Surgery

Objective: Rare disease

Background: Soft tissue sarcomas (STS) account for approximately 1% of adult malignancies, with 50 to 60% occurring in the extremities. Liposarcoma is the most common type of STS and represent about 20% of total adult sarcomas. There are rare syndromes associated with increased risk of developing STS. Further, chemical compounds such as chlorinated phenols and a few chemotherapeutic drugs have been linked to STS, along with ionizing radiation. Nevertheless, the etiology is uncertain for most of these lesions.

Case Report: This report details 2 cases of metachronous bilateral STS of the lower extremities. The first of these presented as a local recurrence of a previously resected right thigh liposarcoma and a new liposarcoma in the left thigh. As mentioned above, among the different subtypes of STS, liposarcoma has the highest tendency for multifocality. The second patient had multifocal metachronous leiomyosarcoma with lung metastases occurring simultaneously with the second presentation. Leiomyosarcoma is another subtype reported to present with multifocal disease.

Conclusions: Despite the rarity of bilateral lesions, their occurrence should not be overlooked in the initial diagnosis and follow-up of the initially detected tumor. Early detection can affect patient survival because their presence predicts unfavorable outcomes.

MeSH Keywords: Liposarcoma • Lower Extremity • Neoplasms, Second Primary • Sarcoma

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/892402

Background

Soft tissue sarcomas (STS) are a group of tumors accounting for 1% of all adult malignancies and up to 2% of all cancer deaths. Predominantly in older males, the annual incidence is about 2 to 4 cases per 100 000 population [1], with a median age of 65 years. STS can occur in multiple forms, but the etiology remains unclear in most cases. However, there are rare syndromes in which there has been increased risk of developing STS, for example, Li-Fraumeni syndrome, Werner syndrome, tuberous sclerosis, and neurofibromatosis type 1. Children with hereditary retinoblastoma due to mutation in RB1 tumor suppressor gene are at high risk of soft tissue sarcomas and osteogenic sarcoma. Chemical compounds such as chlorinated phenols and a few chemotherapeutic drugs have been linked to STS, as has ionizing radiation, (e.g., 3 to 15 years after irradiation for lymphoma, cervical cancer, testicular cancer, and breast cancer) [2]. About two-thirds of all STS arise in the limbs, with up to 50% located in the lower limbs, half of which arise in the thighs. The next most common sites are the upper extremities, followed by the torso, head, and neck [3,4]. Of the extremity and trunk wall STS, almost one-third are superficial, with a median diameter of 9 cm. One-tenth of STS patients have metastasis at time of diagnosis, mainly in the lungs. STS has a poor prognosis, and about one-third of patients die, most commonly those with lung metastasis [5].

Case Report

Case # 1

A 44-year-old man, with history of right thigh liposarcoma, presented with local recurrence at the site of previous resection. The initial presentation had been 2 years prior to this at a different facility, and he was treated by tumor resection and adjuvant radiation therapy. Histopathology of the resected tumor was interpreted as liposarcoma. The patient reported a 5-month history of increasing swelling at the site of the surgical scar. Local examination of the right thigh revealed a hard, fixed, non-tender 20×15 cm mass. Laboratory work-up was unremarkable. Magnetic resonance imaging (MRI) of the right thigh showed a large lesion measuring 18×8×7.5 cm, in the mid-thigh just adjacent to the femoral cortex, without obvious bone destruction, findings in keeping with a recurrent neoplastic process (Figure 1.). The left thigh, which was included in the imaging field, showed an occult mass 10×6×4.6 cm in the posterior aspect of the mid-thigh, highly suspicious of another sarcoma (Figure 2). A CT scan of the chest, abdomen, and pelvis was done as part of the metastatic work-up and revealed no distant metastases. Per multidisciplinary tumor board protocol, a decision was made to offer 50 Gy in 25 fractions as neoadjuvant radiotherapy followed by radical

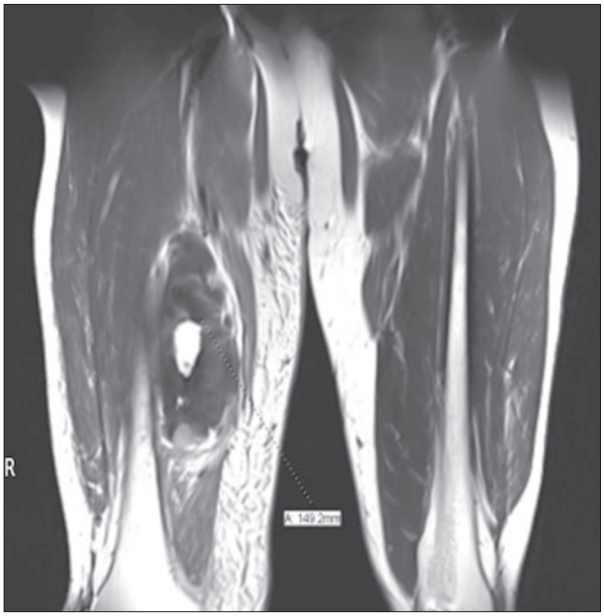

Figure 1. MRI of right thigh: A large mass lesion measuring 18×8×7.5 cm, in the mid-thigh just adjacent to the femoral cortex without obvious bone destruction.

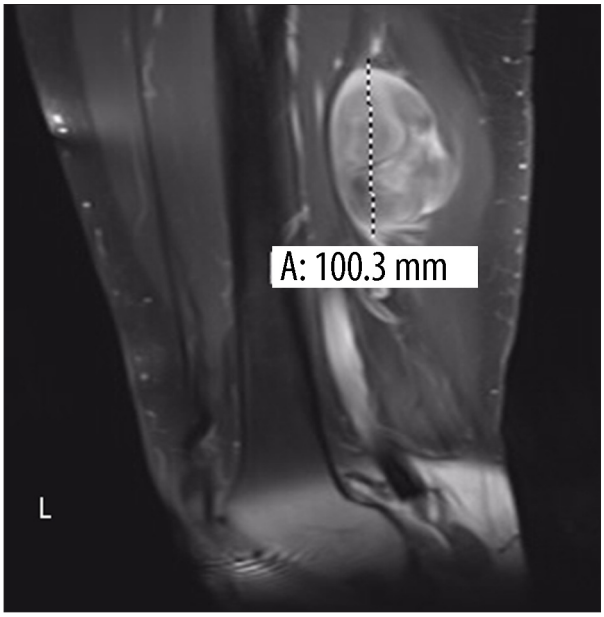

Figure 2. MRI of left thigh: Incidental mass which was highly suspicious of another sarcoma 10×4.6×4.6 cm in the posterior aspect of the mid-thigh.

resection for the right thigh lesion. However, the final histopathology of the right lesion revealed differentiated liposarcoma, French Federation of Cancer Centers (FNCLCC) grade 2, with clear resection margins. The deep intramuscular tumor measured 15.5×9.0×8.0 cm (pT2b), (Figure 3, Case 1). A month later, the patient underwent radical resection of the left-side lesion, and the final histopathology revealed a well-differentiated

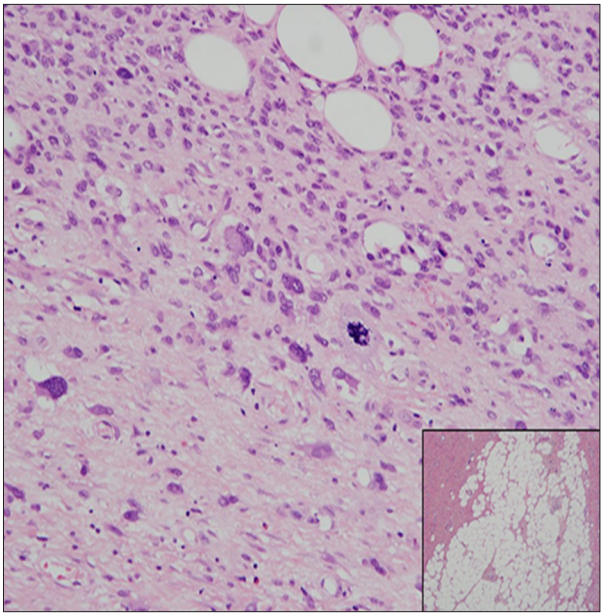

Figure 3. Case 1 – Increased stromal cells pleomorphic hyperchromatic spindle cells and mimotic activity. Inset: Adipocytes separated by thickened fibrous septae containing atypical hyperchromatic spindle cells.

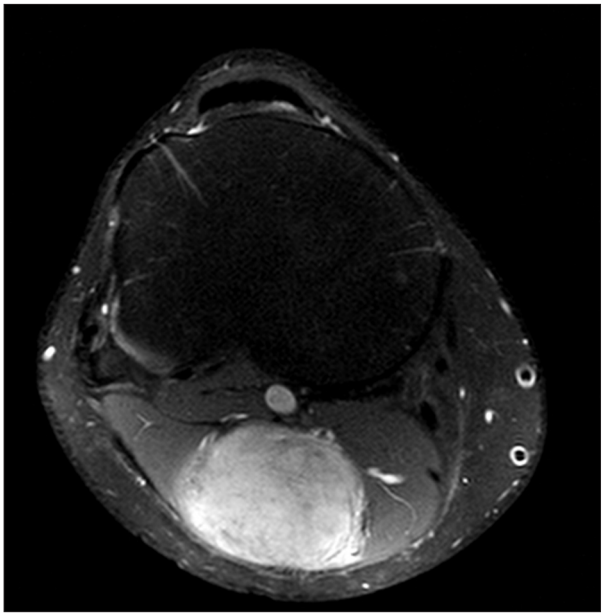

Figure 4. Right thigh MRI showed a 6×4×3 cm well-defined capsulated heterogeneous soft tissue mass lesion in posterior aspect of the right knee behind the popliteal vessels with extra-tumor stranding and infiltration of nearby muscle with no evidence of involvement of the popliteal fossa neurovascular bundle.

sclerosing type liposarcoma, of FNCLCC tumor grade 1, with deep intramuscular location. Currently, the patient is receiving 50 Gy/25 fractions to the left thigh, boosted by 16 Gy/8 fractions to the tumor bed.

Case # 2

The second case is of a 58-year-old man with a 3-month history of left thigh mass. A lesion had been resected at another health care facility 2 years earlier. Histopathology confirmed leiomyosarcoma. The patient noticed a new mass at the surgical site 6 to 7 months later. He underwent resection of the recurrent thigh mass with pathological confirmation of recurrent leiomyosarcoma. The patient subsequently had received 33 fraction of 60 Gy of radiation. On 1-year follow-up he was found to have 3 pulmonary metastases and a new lesion in the right popliteal area. He underwent metastasectomy of the pulmonary lesions, and histopathology confirmed metastatic leiomyosarcoma. Biopsy of the right popliteal mass showed malignant spindle cells consistent with recurrent leiomyosarcoma. Right thigh MRI showed a 6×4×3 cm well-defined capsulated heterogeneous soft tissue mass lesion in the posterior aspect of the right knee behind the popliteal vessels, with extratumoral stranding and infiltration of nearby muscle. There was no evidence of involvement of the popliteal fossa neurovascular bundle (Figure 4.). Subsequently, the patient underwent radical resection of the popliteal mass. Histopathology revealed malignant leiomyosarcoma, grade III, with intermediate lymphovascular invasion and negative margins.

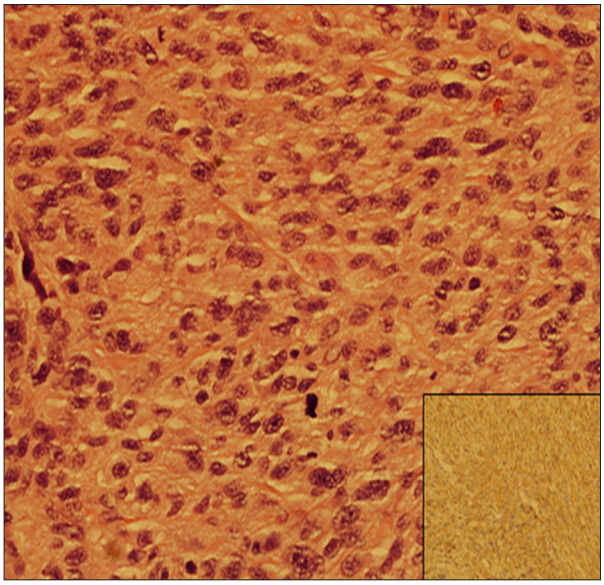

Figure 5. Case 2 – Sarcoma showing tumor giant cells and mitotic activity. Inset: Immunhistochemistry (Caldesmon) showing positive standing, leiomyosarcoma.

The tumor measured 8×4 cm (ypT2b (Figure 5, Case 2). The case was discussed at a multidisciplinary tumor board and it was decided a PET CT would be done, and this did not show any metastases. The patient subsequently received 50 Gy in 25 fractions to the right popliteal fossa with boost of 10 Gy in 5 fractions.

Table 1. Studies reporting STS with associated neoplasm.

Study	Year	Number of patients	Patients with multiple neoplasms
Hartley et al. [13]	1993	310	30 (9.68%)
Merimsky et al. [12]	2001	375	28 (7.5%)
Tateishi et al. [11]	2005	406	35 (9%)
Fernebro [5]	2006	818	164 (20%)

Discussion

Bilateral STS are very rare. A second primary STS occurring in a previously diagnosed adult STS patient has, however, 12.5-fold the risk of a similar lesion occurring in a person with no history of the disease [6]. Children with STS who have been treated with radiotherapy have a nearly 8-fold risk of developing a second malignant neoplasm, including bone and STS [7]. The rate of synchronous/metachronous neoplasms is 7.5% in STS patients compared with 1% in the general cancer population [8]. As per Grobmayer et al., the annual incidence of a non-radiation-induced second primary STS is low, and reported to be 4 per 10 000 population [6]. The reason behind this occurrence remains unclear regarding the etiology of the bilateralism. Possible etiologic factors for the development of second lesions include irradiation effects, exposure to other carcinogenic agents, and genetic predisposition (Recklinghausen neurofibromatosis and chronic lymphedema are possible contributing factors) [9,10].

However, our patients only had a history of radiation as therapy for the primary tumor. In a study by Daigeler et al., 4 out of 1201 (0.33%) cases presented with symmetrical bilateral soft tissue sarcoma of the extremities [9]. Tumors identified in the study were 2 leiomyosarcoma, 1 storiform-pleomorphic type malignant fibrous histiocytoma (MFH), and 1 clear cell sarcoma. In the Daigeler et al. study, the median interval between diagnoses was 3 years. It is worth mentioning that 1 patient in the study had a familial predisposition, another had a history of radiotherapy to the tumor site, and a third had a history of chemotherapy. The fourth patient had a history of leiomyosarcoma of the uterus before the lesions in the thighs, which makes metastasis likely. Three out the 4 patients had died within 4 years after the second tumor, suggesting poor prognosis in such cases. In a study by Fernebro et al., 164 cases out of 818 [20] developed additional primary malignancies preceding or following the STS, with such additional malignancies occurring in a range of 10 years before to 4 years after the STS diagnosis [5]. The primary malignancies that developed before sarcomas were breast cancer, prostate cancer, and melanoma. Fifty-nine and 25 patients out of a total 90 had upper and lower extremity sarcomas, respectively, after the primary sarcoma. The primary malignancies that developed after STS diagnosis and treatment were prostate cancer and colorectal cancer, and 68 and 36 out of total 113 had upper and lower extremity sarcomas, respectively, before the new-onset malignancy. A second STS developed in 7 patients on average 4 years after the primary sarcoma; 2 of these had a third STS. Six of those 9 tumors had the same histopathological subtype, and 3 were of a different subtype than the original STS. Interestingly, among the 96 patients who developed other malignancies following STS, 23 had been exposed to radiotherapy and 4 to chemotherapy; therefore, in this study radiation and chemotherapy only explains secondary malignancy in 27 patients, which is only 28% of the 96 total patients. Knowing that this study excluded hereditary syndromic causes of STSs, we are again back to the conclusion that most other malignancies before or after STSs are not explained. In the same study, we noticed that the lowest rate of second malignancies was with synovial sarcomas (10%), which is similar to the conclusion that Tateishi et al. [11] reached. On the other hand, second malignancies occurred mostly with malignant peripheral nerve sheath tumor (MPNST), which is in contrast to the conclusion reached by Merimsky et al. [12] and Tateishi et al. [11] regarding MFHs, including myxofibrosarcoma being foremost. However, all studies we looked at concluded that age plays a critical factor in developing second malignancies, especially after the age of 65 (Table 1.).

In 2010 Picardo et al. [8] reported a case of bilateral symmetrical metachronous myxofibrosarcoma of the buttocks. The patient developed a contralateral lesion 30 months after the excision of the first one. The author suggested the possibility of the second tumor being a recurrent sarcoma of the same clone or satellite metastasis, although the disease-free interval was 30 months. This argument relies on the demonstration by Antonescu et al. [14] of possible soft tissue metastasis from myxoid liposarcoma. Another study that supports the idea of metastasis, by Fernebro et al., found that in 4 out of 10 patients with multifocal STS of the extremity, the second sarcomas were metastases: 3 MFH and 1 liposarcoma [5].

Park et al. reported a case of liposarcoma of left thigh and Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) of the contralateral proximal tibia, which presented 2 years and 6 months after excision of the liposarcoma [15]. The patient received radiotherapy for the liposarcoma but no chemotherapy,

Table 2. Reported cases of multifocal STS.

Study	Year	Number of patients	Sarcoma subtype
Ackerman [19]	1943	1	Liposarcoma
Georgiades et al. [20]	1969	1	Liposarcoma
Blair et al. [16]	1998	16/1423	Liposarcoma; MFH; angiosarcoma
Antonescu et al. [14]	2000	6	Liposarcoma
Fernández-Aceñero et al. [18]	2007	2	Liposarcoma
Fernebro et al. [5]	2008	20	MFH; leiomyosarcoma; lipaosarcoma; MPNST
Vreeze et al. [17]	2010	15/331	Liposarcoma

because it was contraindicated due to cardiomyopathy. Although it was thought at the beginning to be a rare type of metastasis (as liposarcoma usually favors retroperitoneum, pericardium, and subcutaneous tissue over bone), histopathological and immunostaining results led to the diagnosis of ES/PNET.

The 2 cases in the present report developed a second primary neoplasm of the same histology. The subgroups of STS who present with multiple primary neoplasms of the same histology are usually categorized as multifocal disease. The multifocality is a very rare phenomenon, observed in about 1% of STS patients [16]. It is more common in the liposarcoma subtype, with estimated incidence rate of 4.5% [17]. Multifocality is defined as multiple similar-histology STS in separate anatomical locations, and before the occurrence of distant metastases. It can present as synchronous or metachronous lesions.

Our first patient presented with local recurrence of the previously resected right thigh liposarcoma and a new left thigh liposarcoma. As mentioned above, among the different subtypes of STS, liposarcoma has the highest tendency for multifocality. The second patient presented with multifocal metachronous leiomyosarcoma, with lung metastases occurring simultaneously with the second presentation. Leiomyosarcoma is another subtype reported to present with multifocal disease. Based on the definition of the STS multifocal disease, the second patient cannot be included due to the presence of lung metastases at presentation.

The controversy persists of whether the phenomenon STS multifocal disease is a true multifocal disease or an unusual pattern of metastatic disease. De Vreeze et al. examined the clonal relation between the multifocal lesions in 15 multifocal liposarcoma patients [17]. They analyzed breakpoint detection at the fusion genes and loss of heterozygosity and found that different lesions in each patient were clonally related. This suggests the metastatic nature of these multifocal lesions. In another study, Antonescu et al. used Southern blot analysis on tumors from 6 patients with multifocal myxoid liposarcomas and verified monoclonality, thus demonstrating that multiple myxoid liposarcomas in the same individual most likely represents metastatic disease [14].

Different results were reported by Fernebro et al. [5], who analyzed multifocal sarcoma lesions from 13 patients using comparative genomic hybridization. When the genomic profiles from the different tumor pairs were compared, 5 pairs showed highly correlated genomic profiles, suggestive of metastatic disease, whereas 8 cases showed different profiles, suggestive of distinct primary STS (Table 2.). Another observation supporting the theory that multifocal STS is actually a metastatic manifestations of the disease is their poor prognosis. Blair et al. found no difference in 5-year survival between patients with multifocal STS and patients with metastatic disease [16].

Conclusions

Despite the rarity of bilateral cases of soft tissue sarcomas, their occurrence should not be overlooked during the initial diagnosis stage and at subsequent follow-up. Early detection of additional lesions is likely to improve the prognosis. Genetic testing might be useful in selected cases. Surgery combined with subsequent radiotherapy is the main modality of treatment.

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