Metachronous multifocal myxoid liposarcoma involving the gastrointestinal tract. Management and literature review

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Abstract

Multifocal soft tissue sarcoma is a rare clinical entity occurring in 1% of patients with extremity soft tissue sarcoma and in 4.5% of patients with liposarcoma. Multifocal disease may arise either synchronously or metachronously and has been associated with poor prognosis. Herein, we have described a rare case of metachronous multifocal myxoid liposarcoma involving the gastrointestinal tract that developed 14 months after the resection of a myxoid buttock liposarcoma. Diagnostic evaluation and management of the patient are discussed along with a review of the relevant literature. We conclude that multifocal myxoid liposarcoma is a rare clinical entity that usually represents metastatic disease with poor prognosis. A thorough imaging and careful physical examination are essential in the preoperative evaluation and postoperative follow-up of patients with myxoid extremity liposarcomas, as these tumors are known to have a tendency to spread toward extrapulmonary sites, frequently without pulmonary metastases.

Key words: Gastrointestinal, myxoid liposarcoma, multifocal, metachronous

INTRODUCTION

Liposarcomas are rare malignant tumors of mesenchymal origin, accounting for 20% of all adult soft tissue sarcomas.[1] Based on morphological features, they are classified into myxoid cell, round cell, well-differentiated, and pleomorphic subtypes.[2] Tumors with mixed histologic pattern are very rare.[3] Several differences in location, age distribution, and clinical behavior have been reported among the histological subtypes.[2] The myxoid variant is the most common subtype,[4,5] accounting for 40% of all liposarcomas.[1] It tends to occur in the deep soft tissue of the extremities, particularly, in the thigh.[1] Retroperitoneal myxoid liposarcomas are very rare.[1] Multifocal liposarcomas are a very rare clinical entity. They can be either synchronous or metachronous[6] and are generally associated with an aggressive clinical course and poor prognosis.[5,7-9] Herein, we have presented a rare case of metachronous multifocal myxoid liposarcoma with good response to treatment. Diagnostic evaluation and management of the patient have been discussed along with a review of the relevant literature.

CASE REPORT

A 69-year-old female presented with a 2-year history of a slowly enlarging right buttock mass. Her past medical history was unremarkable, except for hyperlipidemia.

Clinical examination revealed a large, non-tender right buttock mass. The remainder of clinical examination was unremarkable. Computed tomography (CT) scan showed a mass measuring 16 × 15 × 14 cm with imaging features suggestive of a liposarcoma [Figure 1]. Full blood count, biochemical investigations, and tumor markers were all within the normal range. The patient underwent a complete resection of the mass. Histological examination showed a myxoid liposarcoma with clear surgical margins. Staging investigations including CT of the chest and abdomen were unremarkable. Since an excision with clear surgical margins had been performed, the patient was not given any adjuvant treatment.

Eighteen months later, the patient was readmitted complaining of abdominal fullness and dull abdominal pain. Physical examination revealed a large, non-tender mass occupying the left abdomen and a cutaneous mass on the upper inner left thigh. CT scan of the abdomen revealed a large retroperitoneal tumor measuring 22 × 12.2 × 17.5 cm with imaging features suggestive of a liposarcoma. In addition, a smaller tumor measuring 7 × 5 cm was detected in the ileal mesentery close to the ileocecal valve [Figure 2]. At exploratory laparotomy, the retroperitoneal tumor was resected with clear margins. Segmental ileal resection was performed along with sigmoid resection, because a second intraperitoneal tumor was found in the sigmoid mesentery. Wide resection was also performed of the subcutaneous left thigh tumor. Histological examination of all specimens revealed a myxoid liposarcoma with 10-15% round cell component. In addition, the histology of the subcutaneous thigh lesion revealed the presence of tumor emboli within small veins. The patient was given postoperative adjuvant chemotherapy with 6 courses of ifosfamide 5 g/m^2 and doxorubicin 50 mg/m^2. Follow-up investigations after completion of chemotherapy were negative for recurrent disease. However, 2 years later, on CT scans, multiple intraperitoneal and left retroperitoneal masses were detected despite the excellent physical condition of the patient. At this point, the multidisciplinary team suggested chemotherapy with 3 courses of ifosfamide 6 g/m^2, followed by 6 courses of doxorubicin 25 mg/m^2. Despite initial stabilization, progression of the disease was noted and the patient was started on new chemotherapy with 6 courses of liposomal doxorubicin with simultaneous administration of granulocyte colony-stimulating factor and erythropoietin. Unfortunately, although the size of the lesions was initially stabilized, the disease progressed again. Finally, on May 2011, a new chemotherapy regimen consisting of trabectedin was started. After the administration of 6 courses, a significant decrease of the lesions' size was noted, and, thus, it was decided to administer 3 more courses. Presently, the patient remains in a stable partial remission of the disease and is scheduled for new investigations.

DISCUSSION

Multifocality in soft tissue sarcoma is defined as the development a soft tissue sarcoma in two or more separate anatomical sites before the manifestation of the disease in common metastatic sarcoma sites, particularly in the lungs.[6,7] Multifocal disease is a rare clinical entity occurring in 1% of the patients with extremity soft tissue sarcoma[10] and in 4.5% of the patients with liposarcoma.[6] There are no significant differences in sex predilection, age, grade, and depth margins between multifocal and unifocal disease.[10] The first reported case of multifocal soft tissue sarcoma dates back to 1934 when Siegmund described a patient with multiple fatty tumors and coined the term

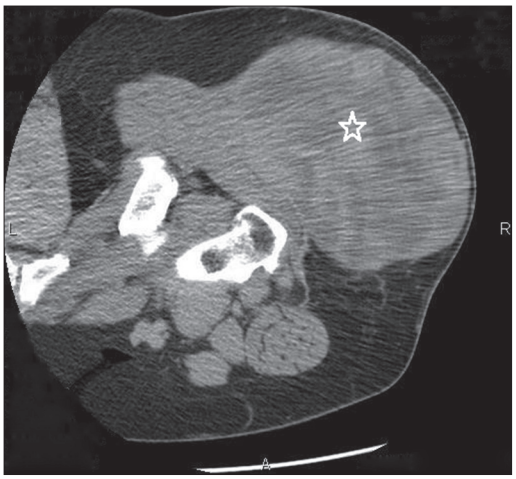

Figure 1: CT scan demonstrating a multilobulated inhomogeneous mass of the right buttock measuring 16 × 15 × 14 cm, consistent with liposarcoma (star)

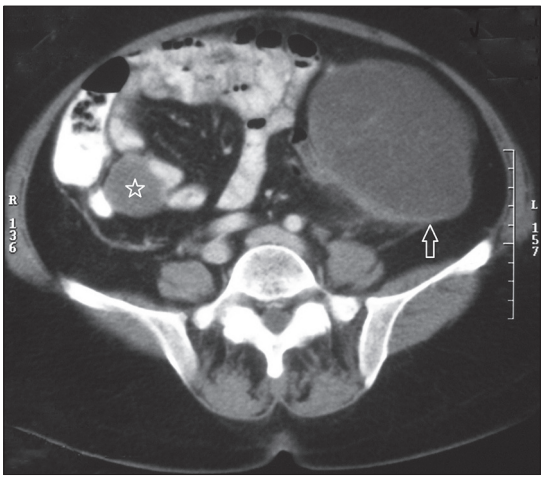

Figure 2: Contrast-enhanced CT scan of the abdomen demonstrating the left retroperitoneal mass (arrow) along with a smaller mass measuring 7 × 5 cm originating from the ileal mesentery (star)

"Lipoblastische Sarcomatose."[11] Since then, less than 50 cases have been reported in the literature, mostly in the form of case studies.[7,9] The largest series was reported in 1962 by Enzinger, who described 20 cases in whom the tumors were exclusively of the myxoid and round cell types, exhibiting a different pattern of spread.[2] The development of multifocal disease is most commonly seen in myxoid liposarcomas and can occur either synchronously or metachronously.[7,12,13] Most patients present with metachronous disease. De Vreeze *et al*., reported that 12 out of 15 (80%) patients included in their study presented with metachronous multifocal disease (mean intervals of diagnosis: 31 months, range: 12-74 months) and only 3 patients (20%) had synchronous disease.[6]

The pathophysiology of multifocal sarcomas is still a matter of debate. It is not clear whether the development of multiple tumors represents new primary lesions or it is a manifestation of metastatic disease.[7,9] It is however important to differentiate between second primary and metastatic disease because a more aggressive approach should be considered in the case of independently arising multicentric liposarcomas.[14] Definitive differentiation requires molecular biologic analysis of the tumor clonal heterogeneity.[10,15] Simultaneous primary liposarcomas are very rare lesions, with only 11 cases reported in the literature.[16]

In our patient, multiple myxoid liposarcomas affecting the small bowel mesentery and sigmoid mesentery, the left retroperitoneal space, and the subcutaneous area of the left thigh were diagnosed 14 months after the resection of the primary buttock myxoid liposarcoma. Resection of all masses with clear margins was performed. Staging investigations showed that the lungs and the liver were not affected by the metastatic disease. Although the histology of the primary buttock mass showed a pure myxoid liposarcoma, the histology of metastatic lesions revealed myxoid liposarcoma with the presences of round cell component of 10-15%. Since the histology showed the presence of tumor emboli within veins in the subcutaneous thigh lesion, we believe that the resected multiple tumors represented metastatic lesions from the primary buttock liposarcoma that was resected 14 months ago. Apart from the presence of tumor emboli in the histological examination, the relatively small period elapsed from the resection of the primary tumor favors the metastatic nature of the multiple lesions. On the contrary, a long interval between the primary and subsequent tumors would rather support a multicentric origin.[14] Histologically, myxoid liposarcomas are characterized by the presence of uniform round to oval primitive nonlipogenic mesenchymal cells and a variable number of small signet-ring lipoblasts in a prominent myxoid stroma.[1]

Myxoid liposarcomas are characterized by the presence of a TLS-CHOP fusion gene, resulting from the t (12;16) (q13-14, p-11) translocation in at least 95% of the cases.[17] The presence of TLS-CHOP fusion is highly sensitive and specific of myxoid/round cell liposarcomas, and, even in the presence of a predominantly myxoid component, the lack of TLS-CHOP rearrangement suggests that the tumor represents a genetically distinct group of liposarcoma.[4] Antonescou *et al*., performed genetical analysis in 6 patients with multifocal liposarcomas and found that the size of the rearranged CHOP fragment was identical in all anatomically separate tumor samples from each patient.[7] Similarly, the sizes of the rearranged bands supported the monoclonality in all cases. Based on their findings, the authors suggested the metastatic nature of distant soft tissue lesions by tumor cells, seemingly incompetent to seed the lungs.[7] Other authors also carried out genetical analysis that supports the metastatic nature of multifocal liposarcomas.[5,6,18] They suggested that a primary curative approach by optional surgical resection combined with radiotherapy for these second tumors would probably not be rational, because the metastatic character of the disease will became clear shortly thereafter,[6] and they also suggested a management tailored for metastatic disease.[10]

Although the lung is the most common site of metastasis reported in up to 80% in liposarcoma patients,[19-22] myxoid liposarcomas are associated with a high tendency for extrapulmonary metastases.[15,20-24] Estourgie *et al*., reported that extrapulmonary metastases were almost three times as frequent as pulmonary metastases in patients with myxoid liposarcomas.[21] Extrapulmonary metastases have been reported in 7-73% of the patients with myxoid liposarcoma.[15,21,24,25] The most commonly affected sites include the retroperitoneum, abdomen, bones, liver, back soft tissues, pleura, chest wall, and pericardium.[15,20,21,23,26] The tendency of myxoid liposarcomas to develop extrapulmonary metastases has significant implications in the clinical management of these patients. Initial evaluation and follow-up investigations should include not only chest CT but also abdominal CT, pelvic CT, bone scanning, and careful clinical examination for possible superficial soft tissue lesions.[8,21,24,27] Additional imaging of the spinal area should also be considered in cases of back pain or any neurological complaints.[21] Furthermore, the possibility of an occult primary tumor in the extremities should be ruled out in patients with trunk liposarcomas.[15]

Myxoid liposarcoma tends to follow a relatively indolent clinical course.[6,22] Guadagnolo *et al*., studied 127 patients with non metastatic myxoid liposarcoma, who were treated with conservation surgery and radiotherapy, and found that the overall survival rate at 5 and 10 years was 87% and 79%, respectively, whereas the local control at 5 years was

97%.[27] Myxoid variants are associated with higher rates of local control as compared to other soft tissue sarcomas.[25]

Complete tumor resection with clear margins is the treatment of choice.[3,9,14,16,20,26] Myxoid liposarcomas are relatively chemosensitive. Jones *et al*., in a retrospective analysis, studied the response to chemotherapy of the different histological subtypes and found a statistically higher response to first-line chemotherapy in patients with myxoid liposarcomas as compared to the other histological subtypes.[28]

The radiosensitivity of myxoid liposarcomas has also been reported.[25,29,30] The radiation sensitivity can be explained by changes in medium-size arterioles obstructing the specific crows feet vascularization, thus including hypoxia with secondary tumor cell death.[30] Patients who were treated with adjuvant radiotherapy had 50% of the risk of developing local recurrence as compared to those who did not receive radiotherapy.[26]

The subset of patients with myxoid liposarcoma patients who present with multifocal disease have significantly worse prognosis.[5,7-10,22] Antonescou *et al*. reported that 5 out of 6 patients with multifocal disease died within 12 months after diagnosis.[7] Patients with soft tissue metastases have 11 times greater chance of dying than those without metastases.[22] The presence of >5% of round cell component is associated with a significantly greater risk of metastatic disease and death.[1,17,20,22,26,31] High-histological grade, presence of necrosis, and P53 overexpression are poor prognostic indicators, but the molecular variability of TLS-CHOP fusion has no prognostic significance.[17]

Since the multifocal liposarcoma carries a poor prognosis, adjuvant chemotherapy and radiation are usually required.[14] However, due to the rarity of the disease, it is difficult to determine the optimal chemotherapy regimen.[8] Anthracycline-based regimens with ifosfamide are usually used.[26] The use of trabectedin has shown clinical benefit and may be considered as an important new option in adult patients with unresectable or metastatic liposarcoma after failure of prior conventional chemotherapy, including anthracyclines and ifosfamide.[32]

In conclusion, we present a rare case of multifocal myxoid liposarcoma, involving the gastrointestinal tract that was diagnosed 14 months after the resection of an extremity primary myxoid liposarcoma. Multifocal liposarcoma is a rare clinical entity, and usually suggests a metastatic disease with poor prognosis. Thorough imaging and careful physical examination are essential in the preoperative evaluation and postoperative follow-up of patients with myxoid extremity liposarcomas, as these tumors are known to have a tendency to spread toward extrapulmonary sites, frequently without pulmonary metastases.

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