CASE REPORT

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Metastatic high-grade myxofibrosarcoma: review of a clinical case

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Abstract

We present the particular clinical and histological features of a metastatic high-grade myxofibrosarcoma (MFS) of the left buttock in a 77-year-old male patient. The tumor was biopsied and surgically removed in order to increase the patient's comfort, due to its increased size and aggressive clinical behavior. Computed tomography (CT) revealed metastases in the pleura and mediastinal lymph nodes, so limb-sparing tumor excision followed by palliative care was the best practice for the patient until the fatal outcome. The histological assessment revealed a tumor composed partly of solid sheets of spindled and pleomorphic cells, partly of areas with prominent myxoid matrix and numerous elongated capillaries. Mitotic figures are frequent, often atypical, followed by numerous giant cells with abundant eosinophilic elongated cytoplasm, resembling myoid cells often multinucleated. A panel of immunohistochemical stainings, including muscle-specific actin (MSA), S-100, CD34, desmin and myogenin were performed with a negative result, which aided excluding other soft tissue tumors like rhabdomyosarcoma and leiomyosarcomas, while Ki-67 was highly expressed in more than 70% of the tumor cells. This tumor received 6 points in accordance with *the Fédération Nationale des Centres de Lutte Contre le Cancer* (modified FNCLCC) and was defined as a high-grade MFS [stage IV, G3 pT2bN0M1, according to the 8th edition of *TNM Classification of Malignant Tumors*, ICD-O 8811/3 in *World Health Organization* (WHO) *Classification* 2013]. Due to the clinical findings combined with the histological profile, the fatal prognosis was expected, though the time period was shorter than predicted, confirming the aggressive nature of the tumor. Even if traditionally was considered MFS as a non-metastatic lesion, recent case reports and studies, including our case revealed that this tumors in fact have the potential to be fatal due to metastatic disease.

Keywords: myxofibrosarcoma, soft tissue tumors, immunohistochemistry, histological features, buttock.

Introduction

The vast family of malignant mesenchymal tumors (sarcoma) represents only 1% of the overall cancers, but even so, it may prove to be a diagnostic and therapeutic challenge in order to prevent life threatening [1]. During present times, important steps in understanding these tumors have been made, especially regarding histological and genetic features [1]. Often growing in a diffuse infiltrative pattern, myxofibrosarcoma (MFS) is a unique subtype of this malignancy, representing approximately 5% of all sarcomas [2]. First described in 1977 as myxoid variant of malignant histiocytoma, MFS was relatively recent recognized as a distinct pathology given the recent use of immunohistochemistry and molecular biology, therefore the clinical features and outcomes are not easy to predict, due to the lack of randomized studies to guide therapeutic protocols [2–5]. The morphology of this tumor reveals a wide spectrum of cell population, pleomorphism and mitotic activity, however, they all have distinct histological features such as myxoid stroma, nodular pattern and curvilinear blood vessels [6]. The low-grade tumor is described as a hypocellular sarcoma with spindled or stellate modified cells and condensation of cells around vessels, sometimes with the presence of pseudolipoblasts [6, 7]. In contrast, high-grade tumors are formed of solid sheets, spindled and pleomorphic cells with frequent atypical mitosis, often accompanied by multinucleated giant cells, areas of hemorrhage and necrotic tissue [6, 7]. The intermediate-grade tumors lend particularities of the other two but in smaller amount, without well-developed solid and necrotic areas or significant pleomorphic cells [6, 7]. Immunohistochemical markers, such as S-100, muscle-specific actin (MSA), alpha-smooth muscle actin (α-SMA), desmin, myogenin and CD34, may prove useful in diagnosis of MFS when they are negative [7]. Ki-67 is able to reflect tumor aggression when it is intensely expressed [7, 8], while high expression of minichromosome maintenance protein 2 (MCM2) may be correlated with a short period until first recurrence [7, 9]. The heterogeneity

of the tumor seems to be a particular feature of MFS, especially in intermediate-grade lesion.

Recent studies have served a considerable amount of information in order to understand features like clinical presentation and biology, but there is much to learn about the prognosis [1–5], the metastatic potential and the therapeutic act, due to the fact that treatment decisions and understanding of the outcomes are based on case reports and retrospective studies [2].

In this paper, we are presenting a rare case of metastatic MFS with particular clinical and histological features, which classified this lesion as an extremely aggressive high-grade tumor, in order to contribute to a better understanding of this potentially fatal malignancy.

Case presentation

In September 2016, a 77-year-old male patient presented to the Department of Plastic Surgery of the Emergency Clinical Hospital of Bucharest (Romania) for a dome-shape tumor mass of the left buttock, which had grown over the last six months. A soft tissue ultrasound was performed and revealed an intramuscular irregular inconsistent tumor measuring 15×10 cm. The patient was sent immediately to the "Prof. Dr. Alexandru Trestioreanu" Oncology Institute, Bucharest, for specific examination. A core-needle biopsy was performed and revealed, using Hematoxylin–Eosin (HE) staining, small areas of mesenchymal proliferation, cells with low and moderate atypia, small fragments of muscle tissue, CD34 positive inside vessels, S-100 negative, α-SMA and unquantifiable Ki-67. This was highly suggestive for a myxoid sarcoma, but it was not enough to establish its malignant nature. After considering the dimensions of the tumor and the biopsy result, the patient was proposed to participate to a multimodal approach of the disease including intratumoral nanoparticle administration and pre-surgery targeted radiotherapy (RT), followed by curative surgery, but he declined. In February 2017, the patient returned to the Department of Plastic Surgery in order for the tumor to be removed. The tumor appeared to be deeply located inside the muscles, causing intermittent regional pain, sometimes paresthesia of the limb and difficulty to the extension of the left thigh. The individual was unable to sleep on his back and had difficulties sitting on the chair. The clinical assessment revealed a larger symptomatic tumor compared to the initial presentation five months ago, measuring 19×17 cm. The skin adjacent to the tumor was elevated with moderate tenderness to palpation, telangiectasia and visible dilated veins, but no palpable regional lymph nodes (Figures 1–3). His medical history revealed ischemic cardiomyopathy, stage II hypertension and *New York Heart Association* (NYHA) I heart failure, for which he was medicated, but no personal or family history of malignant tumors. The routine blood tests revealed moderate anemia (8.2 g/dL) and leukocytosis (15 000/μL), without any sign of infection and accompanied by intermittent low-grade fever. The chest–abdomen–pelvis computed tomography (CT) with contrast agent identified bilateral pleurisy at the base with small atelectasis on the left and a low density nodular tumor located on the left mediastinal pleura near the emerging left pulmonary artery, measuring 3×2 cm (Figure 4), with a suggestive aspect of metastasis, some mediastinal lymph nodes atypical enlargement, splenomegaly, hepatomegaly and a massive intramuscular low density tumor of the left buttock, measuring 20×18×14 cm, with fluid/semifluid densities and small iodophilic areas, which infiltrates inside the pelvis along the piriformis muscle (Figures 5 and 6). The echocardiography revealed moderate pulmonary hypertension (systolic pulmonary pressure – 59 mmHg at rest) and normal systolic function (50%).

A limb sparing surgical procedure was performed under general anesthesia. An elliptical skin incision was performed measuring 15×5 cm, which was included in the postoperative histological sample. After dissection, a giant brownish intramuscular tumor was revealed, with macroscopic normal subcutaneous tissue, located beneath the superficial fascia, infiltrating the muscles of the buttock region, along the fascia of the piriformis muscle (Figure 7). At the surface, the tumor appeared smooth, while becoming infiltrative in the deep. The sciatic nerve was preserved. For a better dissection, the tumor was punctured and three liters of semifluid necrotic brownish mass were evacuated using syringes and sent to cytological and bacteriological exams. The tumor was resected with a 2 cm safety margins, including the piriformis muscle, part of the gluteal medium and maximum muscle, without the certainty of full removal at the superior deep pole of the tumor, which appeared on the CT to be communicating with the pelvic cavity. Two-aspiration drainage were mounted and the wound closed using separate absorbable sutures. No reconstructive procedure was required. Dressing was applied. The tumor comprising muscle, fascia and skin was sent for histological assessment.

The macroscopic aspect of the histological sample revealed 70% of necrotic tissue (yellow and pale gray areas) on a sagittal section along the broadest diameter, also fragile brownish muscular, myxoid and gelatinous tissue and apparently well demarked on the surface and infiltrative in depth. The microscopic assessment revealed a tumor composed partly of solid sheets of spindled and pleomorphic cells, partly of areas with prominent myxoid matrix and numerous elongated capillaries (Figures 8 and 9). Mitotic figures are frequent, often atypical, followed by numerous giant cells with abundant eosinophilic elongated cytoplasm, resembling myoid cells often multinucleated (Figures 10 and 11). A panel of immunohistochemical stainings, including MSA, S-100, CD34 (positive in slender tumor vessels – Figure 12), desmin and myogenin were performed with a negative result, which aided excluding other soft tissue tumors like rhabdomyosarcoma and leiomyosarcomas, while Ki-67 was highly expressed in more than 70% of the tumor cells (Figure 13). This tumor received 6 points in accordance with the *Fédération Nationale des Centres de Lutte Contre le Cancer* (modified FNCLCC) as follows: 2 points for tumor differentiation, 2 points for mitotic counts (10–19 mitoses per 10 high-power fields) and 2 points for more than 50% necrosis of the tumor. The excision margins were R0 (microscopically negative margins), except the superior proximal deep pole of the tumor which was expected R1 (macroscopically complete resection with microscopically positive margins). The lesion had morphological features of a high-grade pleomorphic sarcoma with myxoid stroma and was diag-

nosed as a high-grade myxofibrosarcoma [G3 pT2bN0M1, according to the 8th edition of TNM *Classification of Malignant Tumors*, ICD-O 8811/3 in *World Health Organization* (WHO) *Classification 2013*].

The drainages were removed two days after surgery, and the patient dismissed after five days, with persistent leukocytosis despite the normal evolution of the surgery wound and no signs of infection. He regained function of the limb, without any residual pain or major dysfunction, achieving a considerable improvement of the quality of life. The patient was advised about the fatal nature of his disease and recommended to start palliative chemotherapy and radiotherapy, but he preferred to spent time with the family. After two months, he presented to the regional hospital accusing pain at the operating site, associated with impaired general state, dizziness, asthenia, visual hallucinations, fecal and urinary incontinence with abdominal pain. The clinical exam revealed local recurrence of the tumor. Symptomatic medical treatment was administered in order to improve general state. Four days after dismissal, he died of general metastatic disease.

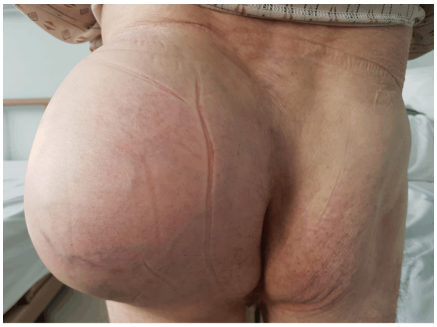

Figure 1 – ***Myxofibrosarcoma: clinical aspect of the tumor – frontal view.***

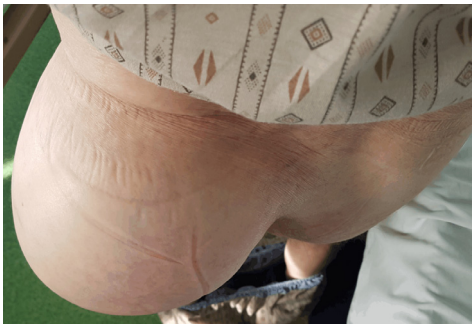

Figure 2 – ***Myxofibrosarcoma: clinical aspect of the tumor – cranial view.***

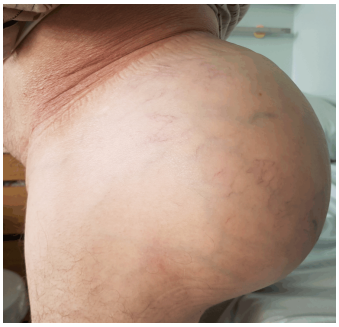

Figure 3 – ***Myxofibrosarcoma: clinical aspect of the tumor – profile view.***

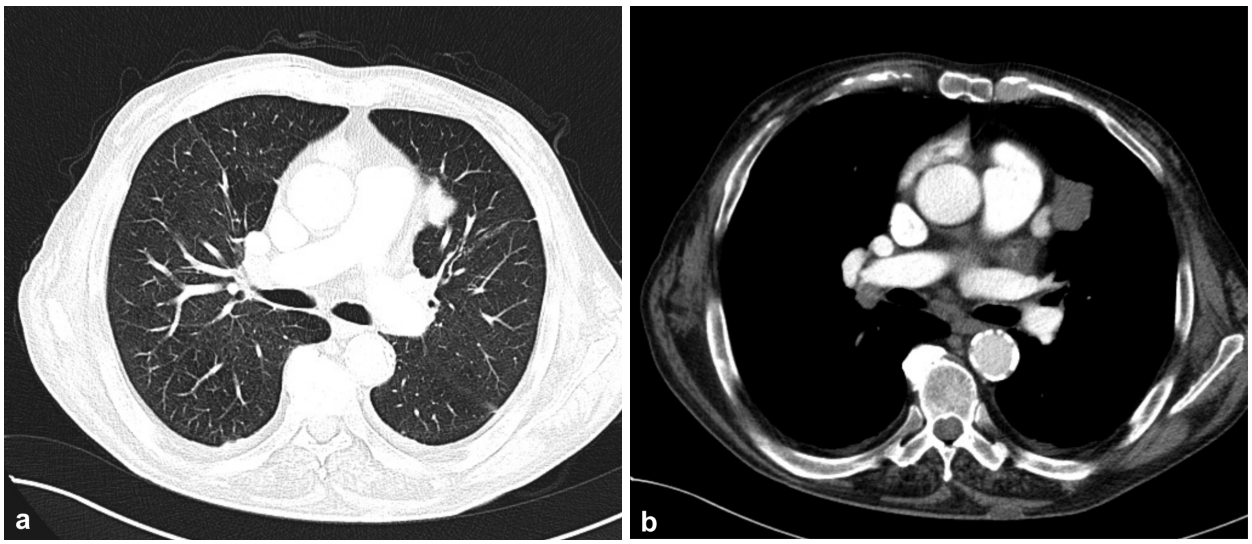

Figure 4 – ***(a and b) Myxofibrosarcoma: CT aspect of the mediastinal pleural metastasis, measuring 3×2 cm.***

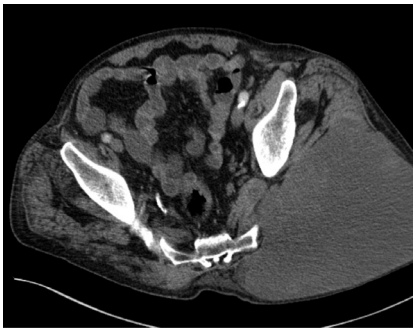

Figure 5 – ***Myxofibrosarcoma: CT aspect of the buttock tumor infiltrating along the piriformis and internal obturator muscles in the pelvic region.***

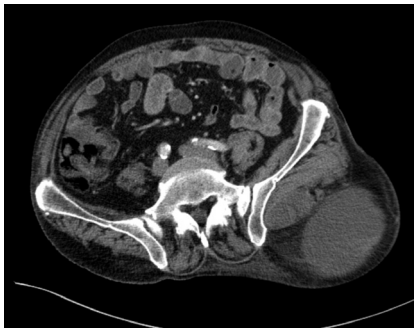

Figure 6 – ***Myxofibrosarcoma: CT aspect of the cranial pole of the buttock tumor.***

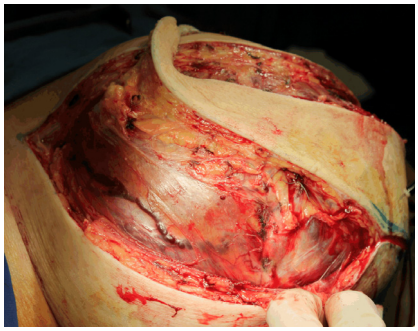

Figure 7 – ***Myxofibrosarcoma: intraoperative macroscopic aspect of the tumor.***

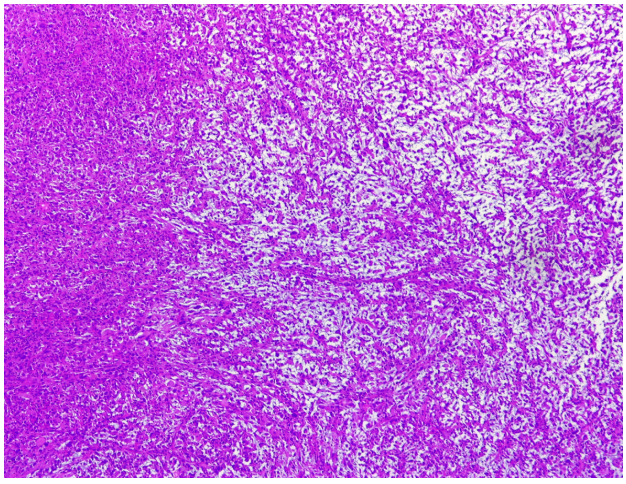

Figure 8 – ***Myxofibrosarcoma: the tumor shows features of a high-grade pleomorphic sarcoma with areas of myxoid stroma (HE staining, ×50).***

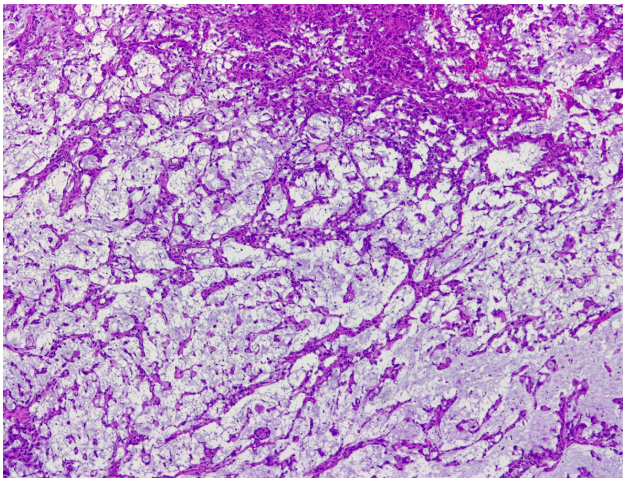

Figure 9 – ***Myxofibrosarcoma: tumor with prominent myxoid matrix (HE staining, ×100).***

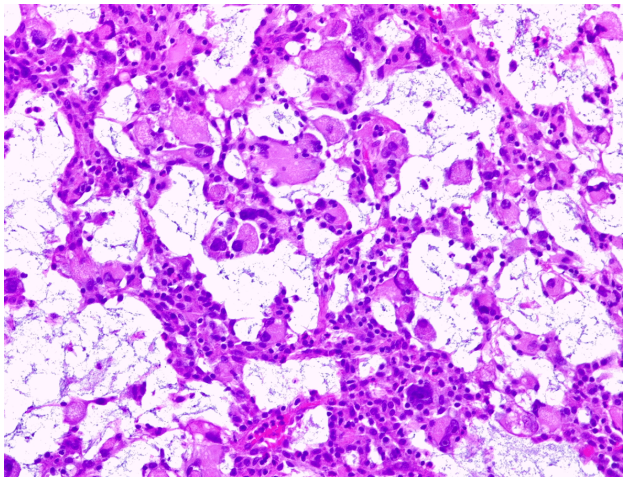

Figure 10 – ***Myxofibrosarcoma: tumor with prominent myxoid matrix and pleomorphic cells, some multi-nucleated, with abundant eosinophilic cytoplasm (HE staining, ×100).***

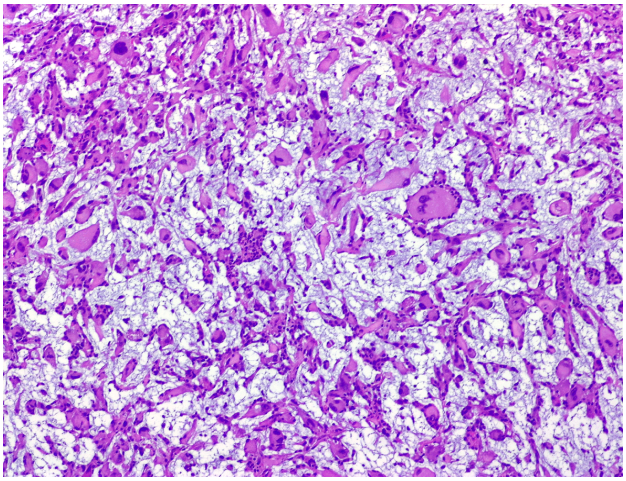

Figure 11 – ***Myxofibrosarcoma: myxoid matrix, with eosinophilic tumoral cells (HE staining, ×200).***

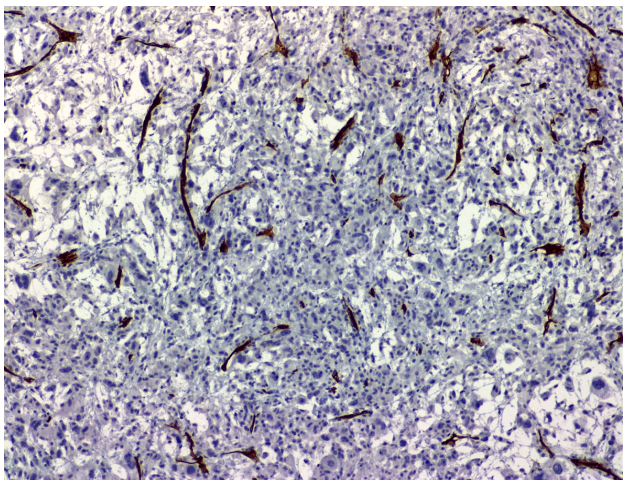

Figure 12 – ***Myxofibrosarcoma: positive staining for CD34 immunohistochemistry (×100) in slender tumor vessels, but negative in tumor cells.***

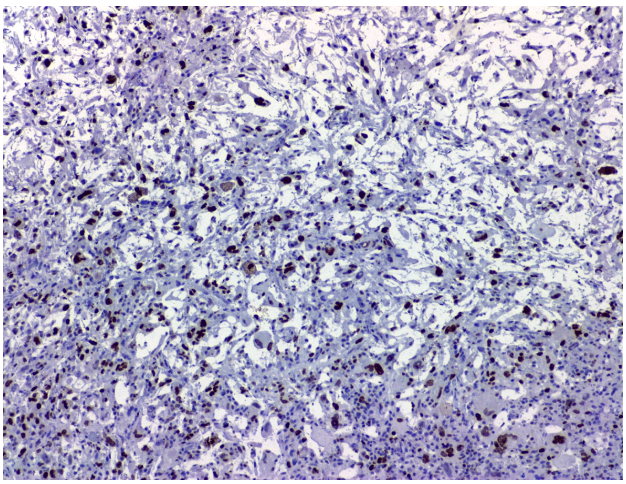

Figure 13 – ***Myxofibrosarcoma: positive staining for Ki-67 immunohistochemistry (×100) with a high Ki-67 index (more than 70% of tumor cells).***

Discussion

Myxofibrosarcoma is considered a rare tumor, representing approximately 5% of all soft tissue sarcoma [2]. It was first described in the literature in 1977, as a myxoid variant for fibrous malignant histiocytoma [10], and was most recently redefined as myxofibrosarcoma, from the histological and immunohistochemical point of view, in 2013, by the WHO [1]. MFS usually develops in extremities of older people (77% of the cases) with a mean age of 65 years, with a predilection for the inferior limb and male patients [1]. Even so, there are few reported cases of MFS developing in the buttock region [2, 7]. In our case, it was very difficult to achieve wide excision due to the insidious boundaries of the tumor, the size larger than 5 cm, the deeply located site, the particularities of the anatomical structures and the communication with the pelvic cavity along the piriformis and internal obturator muscles. There are other regions which represents real challenges for the surgeon in order to obtain R0 margins, like head and neck, trunk, sinonasal, retroperitoneum or heart [2, 11]. Kayser *et al.* reported the first case of MFS arising at the site of a bone infarct, which required above-the-knee amputation [12]. Given the fact that bone infarct may be associated with plates and screws osteosynthesis, with further negative impact also in renal impaired patients [13–17], such complications have not been reported in the literature [18, 19].

The most common clinical presentation is a slow growing painless tumor [2], which can be located subcutaneously, presenting as a multinodular form, or deeply as a single mass between the fiber muscles underneath the superficial fascia [6]. In our case, the tumor became painful due to compression of the nearby structures, which was related to the rapid growth of the mass, up to 7 cm in the last five months before surgery, describing an aggressive clinical behavior. This was correlated with the imagistic result that revealed metastatic disease with the presence of modified mediastinal lymph nodes and left pleural mass, which could have been causing pulmonary hypertension. Also, the routine blood exam revealed persistent leukocytosis associated with splenomegaly, hepatomegaly identified on the CT exam and no signs of infection which was considered a paraneoplastic syndrome. This is supported by Ruka *et al.*, who revealed in a study that significant blood cell count alteration may be commonly encountered in soft tissue sarcomas [20] and by Fong *et al.*, who reported a case of MFS associated with significant leukocytosis, splenomegaly and hepatomegaly [21]. It is well known that MFS is usually associated with high rates of local recurrences, between 16–54% [22, 23], but the presence of metastases is low, between 20% and 25%, usually associated with histologically high-grade tumors [23]. However, a small number of low-grade sarcomas have a risk of 2–10% of metastasis [24], but these rates may increase due to the possibility of acquiring a higher grade for the local recurrences [1]. The most common site is the lung (almost 80% of the cases according to Brennan *et al.*) [3], followed by the pleura, lymph nodes and bones [23]. To our knowledge, there are only 14 case reports until present of metastatic MFS, making our case the fifteenth, though there are some papers that presented cases of metastases without specifying the site or if it was associated with recurrence of the tumor: 14 cases reported by Mentzel *et al.* [6], 10 cases of primary metastatic MFS reported by Huang *et al.* [4] and some cases in a study reported by Merck *et al.* [5]. Therefore, MFS can metastasize and lead to a fatal end, even if it is a small chance, especially in patients with advanced stages of chronic kidney disease associating or not diabetes mellitus [25–28]. In order to diminish the chances for this to occur, it is important to establish a correct early diagnosis and to approach the disease systematically. Imaging followed by biopsy could orientate the diagnosis or even establish the type of soft tissue sarcoma, but the most certain results will be obtained after surgical removal of the tumor followed by histological assessment.

Using magnetic resonance imaging (MRI), Kaya *et al.* described for the first time the "tail sign", which represents an unusual signal infiltration along the fascia and corresponds to the histological infiltrative growth pattern of MFS [29]. Even if the MRI is the best imaging option, CT is also effective in soft tissue tumor diagnosis, especially for those located near the presence of air, such as retroperitoneum or thoracic sarcomas. In our case, we preferred this technique associated with ultrasound, in order to increase the comfort of the patient, which was unable to sit on his back for a large amount of time and delivered sufficient information to plan the surgical procedure. In order to establish the malignancy of the tumor, fine-needle aspiration or core biopsy is required, though in some cases the samples are not enough to describe the type of tumor and accurate grading, as the example of our case [1, 30].

From the histological point of view, in order to reveal MFS, a series of general parameters must be present like spindled shaped cells, elongated, pleomorphic nuclei, abundance of curvilinear vessels with thin walls and myxoid matrix [7, 31], and also some variables depending on the tumors grade, as follows: low-grade tumors are associated with small amount of cells and large amount of myxoid tissue, while high-grade tumors present with large population of cells, less myxoid matrix, multinucleated giant cells, increased mitotic index and important areas of necrotic tissue [6, 31]. In our case, among the general histological aspects of MFS, there were also 70% of necrotic tissue, followed by frequent atypical mitoses, myoid multinucleated cells with elongated eosinophilic cytoplasm and pleomorphic cells. In some cases, there are spindled or eosinophilic cells that may present MSA or α-SMA, which could indicate myofibroblastic differentiation, but in our case this markers were negative, along with S-100, CD34, desmin and myogenin, therefore helping in setting the correct myxofibrosarcoma diagnosis [31]. A series of other pathologies like liposarcoma, desmoid fibromatosis, angiomyxoma, myxoid dermatofibrosarcoma protuberans, rhabdomyosarcoma and leiomyosarcoma could share some of the histological aspects of MFS [7], but in our case, the presence of a massive Ki-67 index for more than 70% of tumor cells, numerous atypical proliferation, and the absence of MSA and S-100 markers underlines the distinct macroscopic, microscopic profile and immunophenotype of a high-grade myxofibrosarcoma. Therefore, in accordance with the latest FNCLCC grading system, we establish this diagnosis with a total score of 6.

It is stated that intermediate and high grade MFS are associated with a higher risk of local recurrences [8], although in this type of tumors staging seems to be more important than grading and variant type in establishing the prognosis [7]. Smith *et al.* reported, in a study regarding soft tissue malignant masses, that tumor grade, size and depth, surgical margins, radiotherapy and patient's age are independent prognostic factors, with the exception of the histological subtype [32]. The overall survival rate at five years is considered between 60–70%, but there are some aggressive high-grade tumors with a poor prognosis [2]. A recent study identified two cell clones, MUG-Myx2b and MUG-Myx2a in a high-grade MFS, which were associated with increased mitotic rate and proliferative index [33]. According to some studies, markers such as p16 and cyclin D1 were not associated as prognostic factors in sarcoma, while intense positive retinoblastoma (Rb) protein was correlated with a lower survival rate [34]. Other studies reveal that p16 is present in 20% of all soft tissue malignancies and can be used to assess different neoplasia associated with human papilloma virus and, but mostly for tumors of the skin [34, 35]. In our case, due to the clinical findings combined with the histological profile, the fatal prognosis was expected, though the time period was shorter than predicted, confirming the aggression of the tumor.

After establishing the diagnosis, wide surgical excision represents the cornerstone of treatment for MFS, but in some cases amputation or radical resection may be required due to local aggressive recurrences [2]. Some studies revealed that adjuvant or neoadjuvant therapies such as radiotherapy may improve local or distant recurrences, but there are no randomized data regarding the benefits in treating MFS [36]. A recent study revealed the benefits of combining intratumoral administration of a radioenhancer (hafnium oxide nanoparticles) and external RT before surgery of patients with sarcomas [37]. There are some cohort studies regarding the role of chemotherapy in improving the survival rate of this disease, but none of them revealed any benefit regarding the evolution of distant metastasis or prognosis [2]. Due to the presence of metastasis, the tumor reported in our paper was classified as stage IV (G3 pT2bN0M1), according to the latest TNM classification, therefore, the aim of the treatment was to remove the primary tumor in order to increase the patient comfort and to assure palliative care, due to the expected fatal outcome.

Conclusions

We presented a rare case of a high-grade metastatic myxofibrosarcoma of the left buttock, with an extremely aggressive behavior and fatal outcome after only two months from surgery. There are a series of distinguishing histological aspects that allows a diagnosis of certainty for this type of tumor and, in most cases, guides the best medical practice in order to improve prognosis. Even if traditionally MFS was considered as a non-metastatic lesion, recent case reports and studies, including our case revealed that these tumors in fact have the potential to be fatal due to metastatic disease. Therefore, early imaging diagnosis, biopsy, wide surgical excision with safety margins, search for metastases and complex histopathological examination are mandatory in order to provide the best results for the patient.

Conflict of interests

The authors declare no conflict of interests.

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