CASE REPORT

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Morphological, imaging and surgical aspects in a complex case of uterine leiomyosarcoma – case report and review of the literature

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Abstract

Leiomyosarcoma is a rare condition so there are relatively few and small case series and no prospective studies to provide clear guidelines regarding management. We report on a case that presents some particularities that further underline diagnostic and treatment difficulties posed by the affliction of such a rare tumor. This is the case of a 43-year-old woman who had a large tumor arising from the uterus, with a spectacular growth rate over a short period. The patient, with congenital spastic tetraparesis and hydrocephalus, came for belly enlargement with rapid increase in size over the previous two months. Physical exam and ultrasound lead to the conclusion of a large abdominal mass. A computed tomography scan showed a mass arising from the pelvis and a large amount of ascites. An exploratory laparotomy was performed and the histopathology report confirmed the diagnosis of uterine leiomyosarcoma. Leiomyosarcoma poses challenging problems regarding histological grading and, due to its rate of growth, real surgical difficulties. Final diagnosis is done by histopathological examination after surgical excision. Frequently, it is late diagnosed when complete removal of the tumor is often impossible.

Keywords: malignancy, smooth muscle, immunohistochemical analysis, management.

Introduction

Leiomyosarcoma is a malignant smooth muscle tumor of the uterus responsible for 30% to 40% of uterine sarcomas, representing 1–2% of all uterine malignancies [1]. Uterine sarcomas (US) are rare, merely 3–5% of all malignant uterine tumors. The overall annual incidence is approximately 17 per million [2, 3]. In studies and systematic reviews hysterectomies or myomectomies performed for a myometrial mass, the prevalence of sarcoma is approximately 0.2% (one in 500) in most studies or reviews, and the range of estimates varies from 0.05% (one in 2000) to 0.28% (one in 352) depending upon the included studies [4–7]. Unlike uterine epithelial tumors, which have comparatively good prognosis, uterine sarcomas are generally characterized by a very poor prognosis, with a high rate of local recurrences and a high rate of metastases [8, 9]. It is a rare condition, so there are relatively few and small case series and no prospective studies to provide clear guidelines regarding treatment or long time management.

Smooth muscle tumors constitute basically a group composed of benign leiomyomas and malignant leiomyosarcomas. Smooth muscle tumors with both atypia and mitotic activity are usually diagnosed leiomyosarcomas on their potential for metastasis but there are lesions that cannot be easily integrated in either category. Extrauterine leiomyosarcomas can occur at any site, although are more frequent in the retroperitoneum and proximal extremities and they are characterized by likeness to smooth muscle but may suffer pleomorphic evolution [10]. Presence of smooth muscle actin is nearly uniform and desmin-positivity frequent. This aspect, together with the lack of KIT expression separate leiomyosarcoma from gastrointestinal stromal tumor (GIST) [11]. Leiomyosarcomas are known to be genetically complex, often found to have chaotic karyotypes including aneuploidy or polyploidy. Recent studies have shown that uterine leiomyosarcomas present frequent mutations in TP53, ATRX, and MED12 [12].

The gross majority of uterine leiomyosarcomas are sufficiently differentiated, at least focally, to allow recognition although they appear malignant on microscopic examination [10]. The diagnostic strategy includes a search for the mitotic index, presence of atypia, and

coagulative tumor-cell necrosis [13]. Uterine leiomyosarcomas are to be diagnosed apart from mitotically active or atypical leiomyomas and uterine smooth-muscle neoplasms with low malignant potential [14]. Presence of coagulative tumor-cell necrosis is decisive and should be distinguished from hyaline and ulcerative necrosis [9]. Usual investigation in leiomyosarcoma histological examination include immunoperoxidase staining is positive for muscle markers: alpha-smooth muscle actin (α-SMA), pan muscle actin (HHF35), h-caldesmon and desmin. A rare number of cases have demonstrated cytokeratin or epithelial membrane antigen (EMA) staining [15]. Histological variants of leiomyosarcoma include atypical leiomyoma that covers a spectrum between leiomyoma and leiomyosarcoma. A mitotically active leiomyoma describes a lesion lacking significant nuclear atypia or tumor necrosis, but with between 5 and 15 mitoses per high-power field (HPF) [16].

Uterine sarcomas have been classified into three main histological subgroups, in order of decreasing incidence: malignant mixed Müllerian tumor (carcinosarcoma, MMMT), leiomyosarcoma (LMS), and endometrial stromal sarcoma (ESS). Each group of tumors exhibits a different pattern of spread, as well pathological features, prognostic factors, and response to treatment. There are in use two grading systems: *Fédération Nationale des Centres de Lutte Contre le Cancer* (FNCLCC) and the *National Cancer Institute* (NCI).

The prognosis of these tumors following surgery varies, with ESS benefiting of a better prognosis compared to leiomyosarcoma or undifferentiated endometrial sarcoma [17]. For aggressive sarcomas, there is expressed interest in adjuvant therapy, which has been centered on the evaluation of systemic agents. However, the rarity of these tumors makes the conduct of prospective trials difficult and no consensus adjuvant regimen has been reached.

Case presentation

A 43-year-old nullipara woman, virgo, uncooperative, oligophrenic, with congenital spastic tetraparesis and hydrocephalus presented at the Emergency Ward of "Elias" Emergency University Hospital, Bucharest (Romania) for gastrointestinal complaints, dyspnea and an abdominal mass with rapid increase in size over a period of two months. The patient had amenorrhea for two months, with no history of genital bleeding.

At physical examination, the patient was in a generally altered condition, pallor was present, but the patient's vital signs were normal. A pelvic examination could not be done because of the spastic position of the patient, who was on her right lateral decubitus with both hips flexed. Abdominally, there was a palpable mass arising from the pelvis to the epigastrium, the upper and lateral borders of the mass could not be made out, the lower margin could not be ascertained, the mass was firm to hard, with restricted mobility and non-tender. Computed tomography (CT) scan (Figure 1) described a large, macronodular, hypodense, approximately 237×222 mm mass arising from the pelvis to the epigastric level, probably concerning the uterus-adnexal area. There was also described hepatomegaly, a single metastatic pulmonary nodule and left hip dislocation. The patient was anemic with hemoglobin 7.7 g/dL and hematocrit 29.2%.

The patient was proposed for an exploratory laparotomy. Intraoperatively clear ascites was present in approximately one liter, a giant uterine tumor, with irregular surface, lobulated, with multiple nodules: 20/15/10 cm (3.3 kg) and four smaller myomas (cumulative size of 7/6/5 cm). The mass had close adhesion to the epiploon, which at that level was edematous; the uterus was globally increased in volume 25/25/15 cm, the ovaries were both polycystic. Total abdominal hysterectomy (along with the tumor) with bilateral salpingo-oophorectomy was performed with the complete removal of the tumor mass (Table 1; Figure 2, A and B).

Table 1 – ***Diagnosis, surgical management and pathology***

Clinical diagnosis	Surgical management	Surgical specimen	Pathology
Uterine tumor	Total abdominal hysterectomy with bilateral salpingo-oophorectomy	Uterus (along with the tumor) Uterine cervix Ovary Fallopian tubes	Giant uterine tumor, with irregular surface, lobulated, with multiple nodules – 20/15/10 cm Weight – 3300 g Uterus – globally increased 25/25/15 cm Ovaries – polycystic Fallopian tubes – preserved structure
Histological examination/ Immunohistochemical analysis			
29 paraffin tissue blocks	Paucicellular, lax and edematous areas, intermixed with dense cellular ones Dense proliferation with fascicular growth pattern (bundles intersect at different angles) Spindle cells – hypertrophic, "cigar-shaped" nuclei, some large, irregular, bizarre nuclei with granular chromatin and small basophilic nucleoli, abundant eosinophilic fibrillary cytoplasm Atypical mitoses – relatively frequent Mitotic index – 2 ↑↑↑ Capillary vessels Reticulin and collagen meshwork surrounding each tumor cell +++ Tumor cells positive for α-SMA CD34 (+) in endothelial cells / (-) in tumor cells ER – diffusely positive in 60% of tumor cells nuclei Ki67 index – 40%		

α-SMA: Alpha-smooth muscle actin; ER: Estrogen receptor.

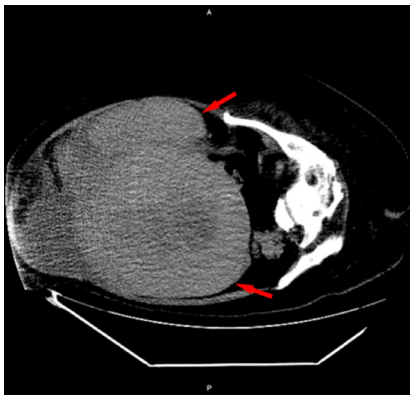

Figure 1 – ***CT scan demonstrating a large, macronodular, hypodense, 237×222 mm mass arising from the pelvis to the epigastric level (red arrows), concerning the uterus and adnexal areas (A – anterior, P – posterior). Note the fact that there was also described hepatomegaly, a single metastatic pulmonary nodule and left hip dislocation.***

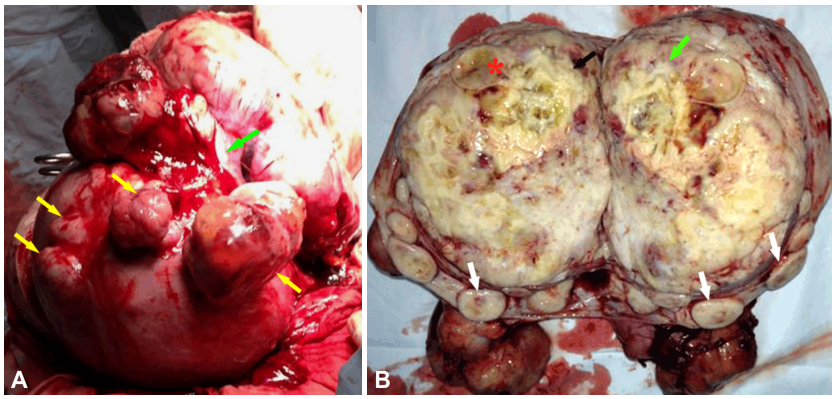

Figure 2 – ***Uterine leiomyosarcoma. (A) Intraoperative post-laparotomy aspect demonstrating a giant uterine tumor, with irregular surface, lobulated, with multiple nodules and four smaller myomas (yellow arrows), close adhesion to the epiploon (green arrow), which at that level was edematous; the uterus globally increased in volume, both polycystic ovaries. (B) Hysterectomy specimen after midsagittal section. The myometrial tumor displays softening (black arrow), gray-yellow color (green arrow), infiltrating aspect, necrosis and cystic degeneration (red asterisk). Note the subserosal leiomyomas (white arrows) with the typical whitish color and the tendency to pop up from the surrounding myometrium when cut.***

The histological examination comprised 29 paraffin tissue blocks (ID No. 281354–281383). One block (No. 281355) was sent for second opinion and specialized immunohistochemistry exam. Histopathological examination revealed: lax, edematous, paucicellular areas, intermixed with dense cellular ones, dense proliferation with fascicular growth pattern (bundles intersect at different angles) composed of large, spindle cells with hypertrophic, "cigar-shaped" nuclei, some large, irregular, bizarre nuclei with granular chromatin and small basophilic nucleoli, abundant eosinophilic fibrillary cytoplasm (Figures 3–5).

There were found relatively frequent atypical mitoses – 15/10 HPFs, rare multinucleate tumor cells and areas of tumor necrosis. Numerous capillary vessels could be seen, some of them dilated with branched or anastomotic rami. There was noted reticulin and collagen meshwork surrounding each tumor cell on Gömöri staining. Tumor cells were intensely positive for α-SMA (imunohistochemical assay for α-SMA), CD34 was positive in endothelial cells and negative in tumor cells highlighting the dense capillary network, estrogen receptor (ER) diffusely positive in 60% of tumor cells nuclei, Ki67 (marker of cell proliferation) positive in numerous tumor cells (Ki67 index 40%) (Figures 6–8).

The histological diagnosis was leiomyosarcoma with mixed areas, grade 2 (FNCLCC score 4 – differentiation 1, mitotic index 2, necrosis 1) ICD-O 8890/3 (Figures 9–11).

Post-surgery evolution of the patient was favorable, as was the general health condition at the one-month visit. Regrettably, we lost the patient at follow-up as there were no further visits and we failed to track the patient probably due to the difficult socio-economic status of the patient.

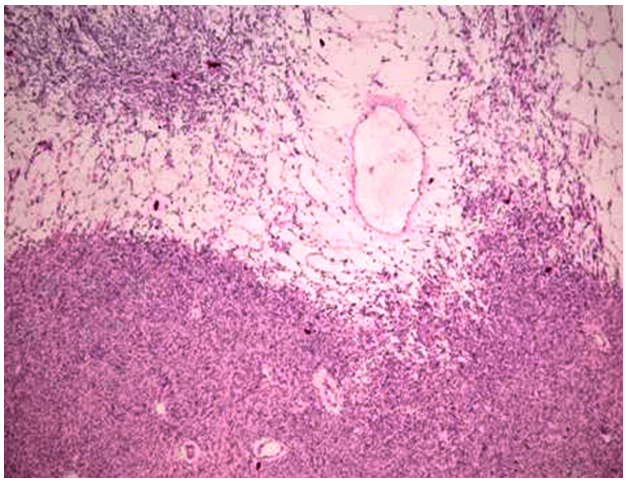

Figure 3 – ***Leiomyosarcoma. Paucicellular, lax and edematous areas, intermixed with dense cellular ones. Hematoxylin–Eosin (HE) staining, ×40.***

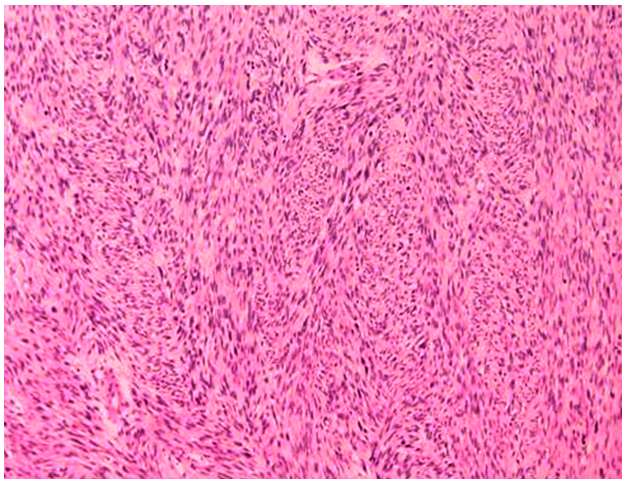

Figure 4 – ***Leiomyosarcoma. Dense proliferation with fascicular growth pattern composed of large, spindle cells with hypertrophic, "cigar-like" nuclei. HE staining, ×100.***

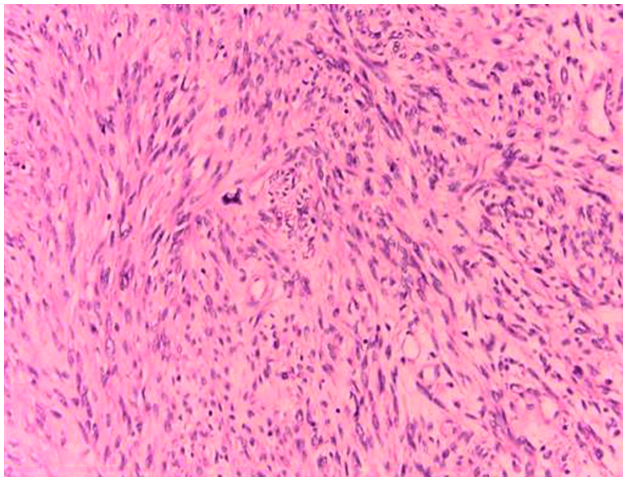

Figure 5 – ***Leiomyosarcoma. Tumor cells with large, irregular nuclei and abundant eosinophilic fibrillary cytoplasm. HE staining, ×200.***

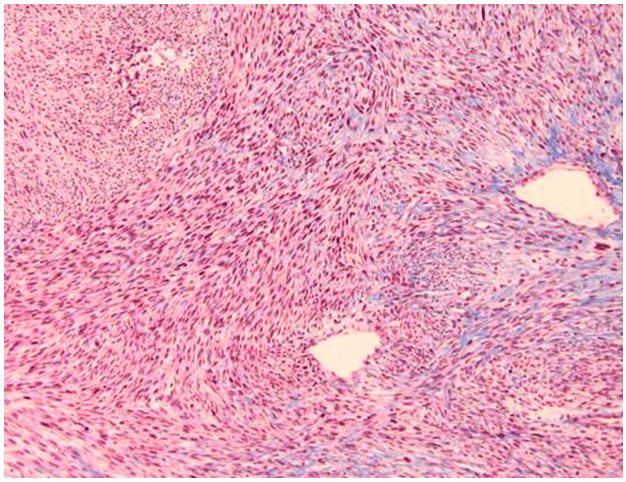

Figure 6 – ***Leiomyosarcoma. Fascicles of tumor cells intersecting at different angles and planes. Note the numerous capillary vessels, some of them dilated and branched. Masson's trichrome staining, ×100.***

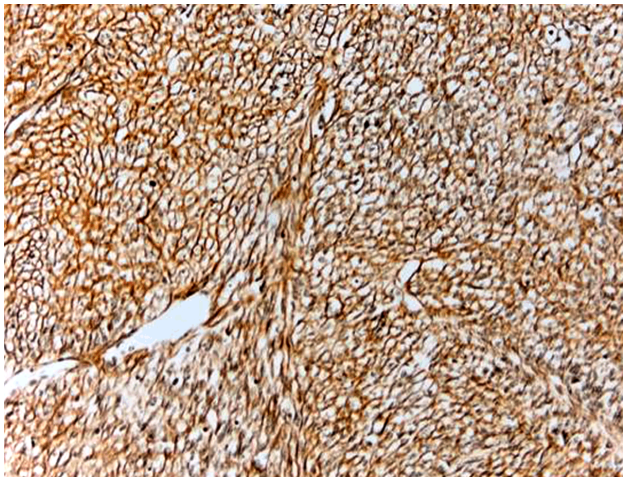

Figure 7 – ***Leiomyosarcoma. Note reticulin and collagen meshwork surrounding each tumoral cell. Gömöri staining, ×200.***

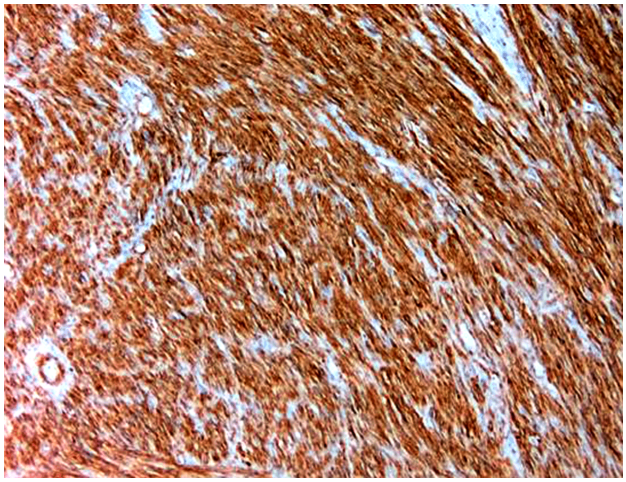

Figure 8 – ***Leiomyosarcoma. α-SMA immunostaining. Tumoral cells are intensely positive for α-SMA, ×100.***

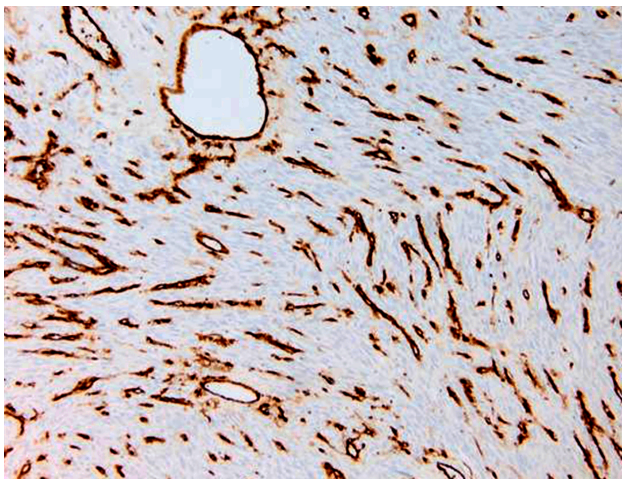

Figure 9 – ***Leiomyosarcoma. CD34 immunostaining. CD34 positive in endothelial cells, negative in tumor cells. It highlights the dense capillary network with dilated and branched vessels, ×200.***

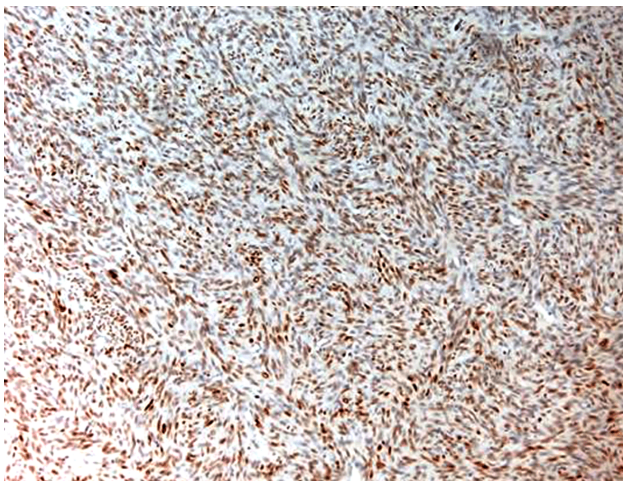

Figure 10 – ***Leiomyosarcoma. ER immunostaining. ER diffusely positive in tumor cells nuclei, ×40.***

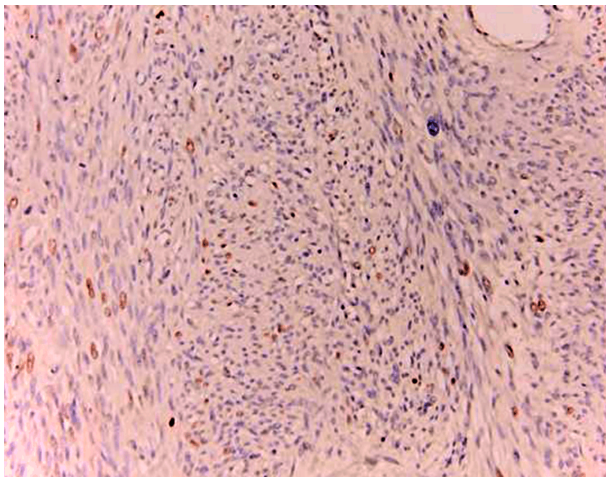

Figure 11 – ***Leiomyosarcoma. Ki67 immunostaining. Ki67 is positive in numerous tumor cells, ×100.***

Discussion

Our paper presents the case of a 43-year-old patient with hydrocephalus, spastic tetraparesis, and impaired cognitive abilities that presented with a greatly distended abdomen and that could only lie in right lateral decubitus. This aspect posed great technical difficulties regarding clinical and imagistic examination, though the patient was largely compliant. Imaging was led by ultrasound exam that found an inhomogeneous aspect with mixed echogenic and poor echogenic areas and irregular vessel distribution within the tumor at color Doppler. The ultrasound characteristics and the fast rate of growth brought to attention the possibility of a malignant uterine lump. However, there were, also, ascites and the ovaries were enlarged with a cystic aspect that was not dissimilar to an ovarian malignancy. There was poor evidence of the tumor limits on ultrasound and a subsequent CT scan was done that showed the real extent of the tumor and the presence of a pulmonary nodule, without underlining suspicion of LMS. Magnetic resonance imaging (MRI) scan, though not highly specific, is the recommended mode of uterine leiomyosarcoma (uLMS) imaging [18, 19] but we had no means of achieving it. Also, a future diagnostic tool may be ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), but current data are limited [20].

As we arose to the decision of surgical intervention, mainly to achieve abdominal decompression, became evident that the team of surgeons and the accompanying anesthesiologists would face a great challenge due to the real difficulty of positioning the patient on the operating table. As myorelaxation was achieved, the operators could further concentrate on the tumor resection. It is important for clinicians to try to resect a tumor as completely as possible as this appears to be the only way to achieve a favorable outcome. Cure rates for patients with disease limited to the uterus range from 20 to 60% depending on the success of the primary resection [21–23]. We performed total abdominal hysterectomy in block with the tumor with bilateral salpingo-oophorectomy completely excising the tumor. The tumor presented intimate adhesion to the epiploon which was edematous and the adnexa were, also, closely bound to the tumor and with edema and inflammation. The histology exam did not find any adnexal spread of the malignancy. Adnexal or lymphatic spread is only present in about 3% of early stage uterine leiomyosarcomas [24, 25]. In a series of 1396 patients, adnexectomy and lymphadenectomy failed to be independent prognostic factors for survival [26]. However, the ovaries are frequently removed in account of age, the small percentage of ovarian metastasis, and the potential for a low-grade hormone-sensitive uterine leiomyosarcoma. A simple hysterectomy with oophorectomy, but without lymphadenectomy, represents standard treatment for early stage uterine leiomyosarcomas. In premenopausal women, a simple hysterectomy (without oophorectomy) can be considered [22]. Histology essays highlighted the presence of α-SMA marker, the high mitotic rate and necrosis that are specific for uLMS. Tumor cell necrosis is only seen in LMS [9, 27]. Our histology exam revealed necrosis as defined for LMS showing a marked transition from necrotic to non-necrotic tumor, without interposed granulation tissue or fibrous tissue and necrotic areas frequently exhibiting preserved nuclei with marked pleomorphism and hyperchromasia and nuclear debris without inflammatory signs [16]. It is very important for the postoperative management of the patient to realize a histological differential diagnosis with leiomyoma. Usually, spindle cell LMS presents elongated cells with eosinophilic fibrillary cytoplasm and elongated blunt-ended nuclei and cells form long intersecting fascicles and frequently display an infiltrative growth into the surrounding myometrium [28, 29]. The lax, edematous, paucicellular areas, alternating with dense cellular ones, the fascicular growth pattern (bundles intersecting at different angles) composed of large, spindle cells with hypertrophic, "cigar-shaped" nuclei, and large, bizarre nuclei with granular chromatin and small basophilic nucleoli and abundant eosinophilic fibrillary cytoplasm that we found at histopathology examination support the spindle cell LMS diagnostic. Also, there were found relatively frequent atypical mitoses – 15/10 HPFs. Rarely, we have to distinguish LMS of leiomyomas with bizarre nuclei (LM-BN). Features that can be seen in LM-BN include large atypical mononucleated or multinucleated cells, karyorrhectic nuclei, prominent nucleoli, nuclear pseudo-inclusions, coarse chromatin, or even increased mitotic activity by the highest count (up to seven mitoses per 10 HPFs). Leiomyomas do not have tumor cell necrosis and they present minimal or no cytological atypia in background non-bizarre smooth muscle cells [30, 31]. It has also revealed positive estrogen receptor in 60% of tumor cells suggesting that would have made the patient susceptible for aromatase inhibitors treatment for consolidation of the surgical achievement. However, a 2010 study failed to demonstrate any real benefits for the outcome [32]. A recently published retrospective study on the use of the aromatase inhibitor letrozole in 16 ER/PR (progesterone receptor) positive uLMS patients revealed clinical benefit in 10/16 patients (partial response in 2/16 and stable disease in 8/16 patients). Also, the use of the aromatase inhibitor exemestane as second line treatment resulted in clinical benefit in 50% of patients. However, no prospective trials testing hormonal therapy in uLMS have been performed [33,

34]. Usual first line chemotherapy is fixed-dose rate gemcitabine plus docetaxel, and adding the angiogenesis inhibitor bevacizumab showed no benefit [35–37].

Although we recommended oncological follow-up the patient failed to comply mainly due to poor socio-economic condition with the only one known relative being her stepmother.

An interesting aspect of this case is represented by the possibility of an X-linked congenital condition such as the ATR-X – alpha thalassaemia-mental retardation syndrome [38] that could explain the anemia in the absence of vaginal bleeding and the mental impairment of the patient. A very recent study established by exome sequencing of uterine leiomyosarcomas there are frequent mutations in TP53, ATRX, and MED12 [12]. It presents itself as an interesting theory the possibility of an X-linked mutation that both could promote leiomyosarcoma and, also, explain anemia, spastic tetraplegia and mental retardation. Other mutations on the X chromosome are also related to hydrocephalus. The vast majority of described cases of ATR-X syndrome affect male patients and are extremely rare and usually milder in women.

Conclusions

Leiomyosarcoma poses challenging problems regarding histological diagnosis and, due to its growth rate, real surgical difficulties. Imaging investigations like ultrasound, MRI and CT are not consistent with leiomyoma differential diagnosis, leaving to the histology exam the leiomyosarcoma diagnosis. Frequently, it is late diagnosed when complete removal of the tumor is often impossible. Owing to advancing science in the complex genetics of the tumor and the future promise of targeted molecular treatment, we may hope for a less bleak outcome for the leiomyosarcoma patients.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Aida Tincuța Petca and Costin Berceanu contributed equally to the manuscript.

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