



# Morphological and Ancillary Features of Uterine Leiomyosarcoma: Case Report

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Mădălina Boşoteanu<sup>1,2</sup>, Raluca Ioana Vodă<sup>1,3</sup> , Mariana Aşchie<sup>1,3,4</sup>,  
Luana-Andreea Bosoteanu<sup>5,6</sup> and Gabriela Izabela Bălţătescu<sup>1,3</sup> 

<sup>1</sup>Clinical Service of Pathology, "Sf. Apostol Andrei" Emergency County Hospital, Constanța, Romania. <sup>2</sup>Department of Pathology, Faculty of Medicine, "Ovidius" University of Constanța, Constanța, Romania. <sup>3</sup>Center for Research and Development of the Morphological and Genetic Studies of Malignant Pathology – CEDMOG, "Ovidius" University of Constanța, Constanța, Romania. <sup>4</sup>Academy of Medical Sciences of Romania, Romania. <sup>5</sup>Elias Emergency University Hospital, Dermatovenerology Department. <sup>6</sup>"Ovidius" University of Constanta, Institute of Doctoral Studies, School of Medicine.

**ABSTRACT:** We report a rare case of giant uterine leiomyosarcoma in a postmenopausal woman, whose diagnosis was initially suspected at the evaluation of the abdominal effusion, and confirmed after the pathological examination of the uterus in association with the ancillary tests. The evaluation of the abdominal fluid showed single or clusters of malignant, round or spindle-shaped cells. On microscopic examination of the surgical specimen, a dense cell proliferation of spindle cells, with moderate to severe nuclear pleomorphism and significant mitotic activity was observed. Immunohistochemical evaluation demonstrated the loss of myocytic differentiation by focal, weakly positive expression of smooth muscle actin and desmin. The data presented in this case emphasize the relevance of the cytological examination, although the latter has only indicative value, especially since it is an aggressive tumor, frequently associated with mutant expression of p53. In our case, the first indication of the presence of uterine sarcoma was given by the presence of atypical cells in the peritoneal fluid.

**KEYWORDS:** Cytology, differentiation, immunohistochemistry, mesenchymal tumor, uterine leiomyosarcoma

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**CORRESPONDING AUTHOR:** Raluca Ioana Vodă, Department of Clinical Pathology, "St. Apostle Andrew" Emergency County Hospital, Constanța, Romania; Center for Research and Development of the Morphological and Genetic Studies of Malignant Pathology – CEDMOG, "Ovidius" University of Constanța, 145 Tomis Avenue, Constanța 900470, Romania. Email: raluca.v1694@yahoo.ro

## Introduction

Uterine sarcomas are rare malignant tumors representing up to 1% of all gynecological cancers and 3% to 7% of the malignant tumors of the uterine corpus.<sup>1</sup> The mean age at the time of diagnosis is 55 years old, which varies depending on the histological subtype.<sup>1</sup> Leiomyosarcomas account for almost 70% of these tumors, with a variable incidence ranging from 0.35 to 0.8/100 000 women.<sup>2–4</sup> In this tumor category, the 5-year survival is 25% to 76% and only 10% to 15% in the case of metastatic disease at the time of diagnosis.<sup>2</sup> Its poor prognosis and the high rate of recurrence require establishment of a correct and prompt diagnosis followed by surgical therapy, which is the most effective, especially in earlier stages. Total abdominal hysterectomy and bilateral adnexectomy are recommended in stage I, followed by adjuvant chemotherapy in higher stages.<sup>5–8</sup> The main peculiarity of this case lies in the suspicion of the diagnosis of uterine sarcoma starting from the cytology of the peritoneal fluid, a diagnosis that was later confirmed by examining the surgical piece. To this aspect is added the loss of the myocytic differentiation of the tumor smooth muscle fibers, which together with the immunohistochemical overexpression of the p53 gene, determines an unfavorable evolution of the patient, resulting in her death.

## Case Report

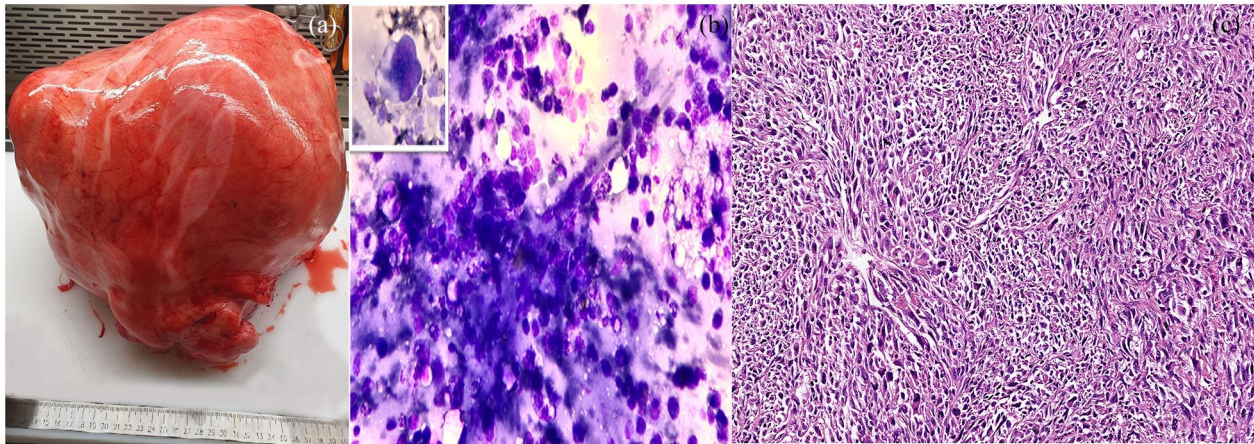
A 53-year-old woman presented to hospital reporting diffuse abdominal pain and abnormal vaginal bleeding. The clinical

examination revealed a painful abdominal mass, as well as metrorrhagia. The abdominal echography revealed the presence of ascites and a large mass of the uterus with ill-defined, irregular borders. Thoracic computed tomography showed multiple round solid masses in the lungs and mediastinum. A paracentesis was performed and 5 ml of abdominal fluid was sent for pathological examination. The cytological evaluation identified isolated or clustered malignant cells, round or spindle-shaped, highly suggestive for sarcoma (Figure 1b). The patient underwent total hysterectomy and bilateral adnexectomy. One month postoperatively, the patient returned with abnormal vaginal bleeding and a vaginal nodular lesion, which had the same microscopical features as the uterine tumor. After interdisciplinary consultations, the oncologist contraindicated cytoreductive therapy due to the presence of distant metastases. The patient died a few months after the last hospitalization.

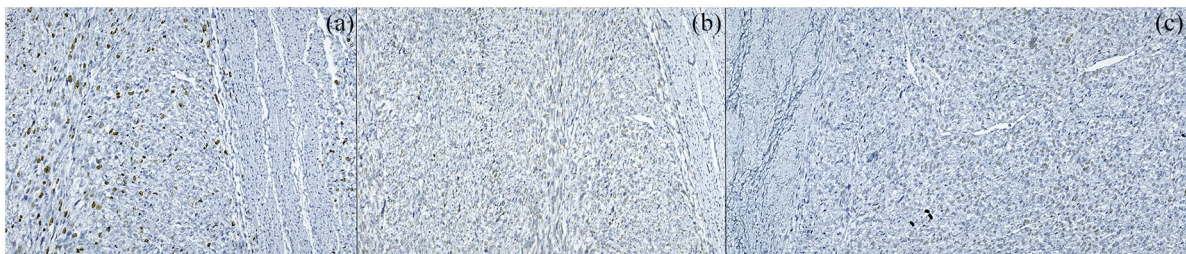
The uterus weighed 10 kg and it was deformed by a giant tumor measuring 28/27/24 cm with polycyclic contour. On cut surface, this was fleshy, fasciculated, with cystic spaces, necrosis and hemorrhage (Figure 1a). The omentum showed white-gray multiple nodules.

Microscopically, the tumor was composed of a dense malignant cell population with fusiform appearance, moderate to severe cytological pleomorphism and an important mitotic activity (12 mitoses/10 high power fields) (Figure 1c). Areas of tumor necrosis were identified, as well as angio-lymphatic invasion. The omental nodules had the same characteristics as





**Figure 1.** (a) Gross aspect of ULMS: enlarged and deformed uterus by a nodular lesion with a maximum diameter of 28 cm. (b) Microscopic features of the cytological exam: round or fusiform malignant cells, isolated or grouped in clusters; in case: a giant multinucleated cell (Giemsa stain; Ob  $\times 100$ ; in case Ob  $\times 200$ ). (c) Microscopic features of ULMS: hypercellular and fusiform proliferation of highly mitotic, pleomorphic malignant cells (HE stain, Ob  $\times 100$ ).



**Figure 2.** (a) Ki-67: intense, diffuse nuclear expression in more than 50% of the tumor nuclei (Immunohistochemical stain, Ob  $\times 100$ ). (b) p16: intense, diffuse nuclear expression in more than 75% of the tumor nuclei (Immunohistochemical stain, Ob  $\times 100$ ). (c) p53: intense, diffuse nuclear expression in more than 80% of the tumor nuclei (Immunohistochemical stain, Ob  $\times 100$ ).

the uterine tumor. Morphopathological features were compatible with high grade uterine leiomyosarcoma FIGO stage IVB diagnosis.

The immunohistochemical tests revealed a positive immunostaining for p16, Ki67 and also the overexpression of p53. Negative immunorexpression for Estrogen (ER) and Progesteron receptor (PR) was noticed, as well as weak focal reaction for Smooth Muscle Actin (SMA) and Desmin (Figure 2).

## Discussion

Metastasis appears mainly by hematogenous routes, explained by the rich vascularization of the myometrium, by trans-tubal route of exfoliated cells from the primary tumor or by direct extension.<sup>6</sup> The study conducted by Tirumani et al<sup>10</sup> confirmed that distant spread is predominantly located in the lungs (74%) followed by the peritoneum (41%). One particularity of the current case is its late diagnosis based on cytologic evaluation of the peritoneal effusion due to direct dissemination to this compartment. Moreover, following the study by Wang et al<sup>11</sup> on cytological aspects in cases of uterine sarcoma, they observed that the presence of malignant cells in the peritoneal fluid of patients diagnosed with leiomyosarcoma is a feature that contributes to the orientation toward a correct diagnosis. This observation, combined with the unfavorable

evolution, is consistent with the findings of the study by Matsuo et al which states an almost double increase in the risk of mortality in uterine sarcoma patients with malignant peritoneal cytology compared to those with negative cytology, with particular implications in dramatically decreasing 3-year survival in cases of uterine leiomyosarcoma.<sup>12</sup>

Immunohistochemistry is an extremely useful tool in differential diagnosis while supporting the high degree and aggressiveness of this malignancy.<sup>13</sup>

The Ki-67 antigen is expressed only in proliferating cells and its increased positivity correlates with the invasion of vascular spaces and with a poor clinical evolution.<sup>14,15</sup> The research conducted by Mayerhofe et al<sup>16</sup> proved that Ki-67 expression was present in 50% of leiomyosarcomas, the difference being significant compared to the other 2 tumor types (negative for smooth muscle tumors of uncertain malignant potential and 8% of leiomyomas). The p16 is a protein integrated in the Ink4 family of CDK inhibitors, being involved in the regulation of the cellular cycle by inhibiting the S phase.<sup>17</sup>

It is useful in differential diagnosis of leiomyosarcoma with smooth muscle tumors of uncertain malignant potential or leiomyomas as it is overexpressed in leiomyosarcomas.<sup>18</sup> In addition, the expression of p16 and PR significantly differs in leiomyosarcomas and atypical leiomyomas, in favor of the first,

advocating the intense positivity of p16 associated with the reduced expression of PR.<sup>19</sup>

An overexpression of p53 protein favors the diagnosis.<sup>13</sup> Immunohistochemical evaluation of p53 biomarker is essential for diagnosis, especially when it is part of an extended panel of antibodies and can provide useful information regarding the prognosis, as its aberrant (mutational) type is associated with a decrease of the overall survival.<sup>13,20</sup>

Smooth muscle actin and Desmin biomarkers highlight the smooth muscle origin for different neoplasms. The study of Demicco et al.<sup>21</sup> proved that their expression may decrease from 99% in well-differentiated tumors to 73% in the poorly differentiated ones for SMA, and from 89% to 50% for Desmin. In the present research, the low expression of the myogenic markers represents the second particularity of this study, because the loss of myogenic differentiation correlates with increased aggressiveness of the tumor and rises difficulties in establishing a correct diagnosis.

Considering that this neoplasm originates from a hormonally active tissue, it is important to study the expression of hormonal receptors, on account of a prognostic and possibly therapeutic impact. The study of Azimpouran et al.<sup>22</sup> concluded that a reduction of ER and PR immunorexpression is associated with an increase of the malignant potential. These deductions are also supported by the current case, where ER and PR are negative.

Corroborating numerous diagnostic tests, the key features of this case were identified: direct dissemination in the abdominal compartment, loss of myocyte differentiation, reduced expression of hormone receptors, the consequence of which was the unfavorable evolution of the patient, excluding chemotherapy from therapeutic options.

## Conclusion

The cytological examination has an orienting, not a certainty value, as a final diagnosis cannot be reached only on the basis of peritoneal fluid cytology. The evaluated immunohistochemical markers highlighted both the loss of myocyte differentiation and the overexpression of the p53 biomarker, results consistent with the aggressive biological potential of high grade uterine leiomyosarcoma.<sup>9</sup>

## Author Contributions

Mădălina Boşoteanu: Reviewing drafts and final approval of the version to be published. Raluca Ioana Vodă: The acquisition of data for the work and writing the manuscript. Mariana Aşchie: Final approval of the version to be published. Luana-Andreea Bosoteanu: The analysis of data for the work. Gabriela Izabela Bălăţescu: Drafting the work.

## Patient Consent

All the examinations and treatments in this case report were clinical routines which were necessary for accurate diagnosis and improved outcome. Informed consent for all diagnostic

measures and treatment options, as well as for the use of the data for scientific purposes was obtained from the patient.

## ORCID iDs

Raluca Ioana Vodă  <https://orcid.org/0000-0002-9396-2350>

Gabriela Izabela Bălăţescu  <https://orcid.org/0000-0003-1910-9797>

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