

CASE REPORT

Uterine malignant leiomyosarcoma associated with high levels of serum beta-human chorionic gonadotropin: A case report

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Abstract

We present the case of a 54-year-old woman diagnosed with uterine leiomyosarcoma that produced beta-human chorionic gonadotropin (β -hCG), evident by both serum and immunohistologic examination. Based on this and similar cases from the available literature, β -hCG-producing sarcomas tend to have poorer prognosis, indicating that β -hCG could potentially be used as a marker of disease status and response to the therapy; however, this association is inconsistent and should be further investigated.

KEYWORDS

gynecologic neoplasms, HCG-beta, leiomyosarcoma, uterine bleeding, uterine neoplasms

1 | INTRODUCTION

Leiomyosarcomas of the uterus have an estimated incidence of 0.64 cases per 100,000 women and are among the commonest uterine sarcomas¹; they are rare and constitute 1% of all uterine neoplasms, being the commonest mesenchymal uterine malignancy.² Although uterine leiomyosarcomas may occur in the third decade of life, they are more likely to appear in women aged between 40–60 years.³ The clinical outcome is invariably poor, and uterine leiomyosarcoma is considered to be a neoplasm of high metastatic potential. Median life expectancy is 2 years from the time that metastases are diagnosed, and 5-year survival rates may vary between 0%–73%.^{2,4,5}

Major prognosis discrepancies have been reported due to inconsistent disease definitions and due to the variability of sample sizes examined; however, a consistent prognostic factor is the extent of the underlying disease.⁶

In order to confirm the diagnosis of leiomyosarcoma, at least two of the three following criteria should be present and confirmed: coagulative necrosis, diffuse nuclear atypia, and increased mitotic rate.⁷ Common presenting symptoms include abdominal and/or pelvic pain and vaginal bleeding; however, the diagnosis is usually confirmed after surgery or by a prior D&C procedure. Furthermore, optimal surgical treatment should include total abdominal hysterectomy with lymph node dissection, the value of which remains controversial, however, due to the low

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incidence of lymph node metastases at rates around 3.5%–7% of cases.^{8,9}

2 | CASE PRESENTATION

In this report, we present the case of a 54-year-old woman of Greek Caucasian origin, gravida 0, para 0, with a body mass index of 41.5 and a history of non-insulin-dependent diabetes mellitus under inadequate control (HbA1c: 6.8%) via oral medication and diet.

There was no other significant medical history or family history of gynecological cancer. The woman had a 2-year history of intermittent meno-metrorrhagia and abnormal vaginal bleeding of variable severity, ranging from minimal spotting to severe bleeding. From the patient's own reports, she was of post-menopausal status (lack of menstruation for at least 1 year), which was later also confirmed via the results of hormonal testing, found in the patient's file, conducted elsewhere prior to the aforementioned clinical manifestations. The symptoms progressively worsened, leading to iron deficiency anemia on presentation (Hb = 9.3 g/dl). Two years prior to the patient's presentation to our team, a lower abdomen MRI scan showed an abnormal signal, indicative of an intramural fibroid with subcutaneous extension, with a maximum diameter of 31 mm. In the 12 months leading to her presentation, the patient had undergone three D&C procedures elsewhere, all of which were negative for any kind of malignancy. Due to the high clinical suspicion of malignancy, another D&C was performed and the diagnosis of leiomyosarcoma was yielded.

The patient underwent Oncology board evaluation as per our team's standard protocol, and oncological staging was subsequently performed via MRI pelvic scan. The scan detected a large tumor with blurred limits and dimensions of 14.5×10.2×9 cm and a small amount of fluid in the pouch of Douglas (Figure 1). A chest computed tomography scan showed multiple lesions in both lungs, compatible with distant metastases, the largest being 16 mm in the upper lobe of the right lung and 11, 17, and 15 mm on multiple locations in the lower lobe of the left lung. Mediastinum and axillary lymph nodes appeared to be of

normal structure. As per the standard protocol followed in our clinic, several serum tests were conducted and subsequently revealed largely elevated beta-human chorionic gonadotropin (β -hCG) levels at 383.3 IU/L (reference normal levels <5 IU/L) with all the other serum tumor markers (CEA, Ca-125, Ca 15.3, Ca 19.9, a-FP) being within normal levels. Despite the patient's post-menopausal status and the fact that pregnancy was ruled out, both due to personal history (no sexual intercourse in the past year) and to D&C histological findings; the patient underwent ultrasonographic imaging, which definitively ruled out that possibility, as is dictated for laboratory findings indicative of pregnancy by the protocol of our clinic.

A total abdominal hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, cytology examination of peritoneal washings, and subcolic omentectomy was performed. Nine and six pelvic lymph nodes were dissected from the right and left side, respectively, in close proximity to the iliac vessels. The uterus was enlarged, and no other obvious lesions were observed during the surgery on the bowel, the omentum, the peritoneum, and the diaphragm. Three weeks later, the β -hCG levels had returned to normal (2.2 IU/L). The patient made an uneventful recovery, proceeded with further Oncology board evaluation, and underwent chemotherapy, however ultimately died 6 months later due to pulmonary embolism.

On gross examination, the uterus measured 18.5×12.8×10 cm, weighed 1.3 kg, and was deformed. The lesion infiltrated the entire myometrium on the fundus of the uterus and extended lower until the endocervix and upon sectioning was solid, of white to light yellow color (Figure 2).

Microscopic histological examination was typical of a high-grade leiomyosarcoma. The tumor infiltrated the myometrium and consisted mainly of highly atypical, dense neoplastic populations of spindle cells, with intense nuclear atypia, deeply stained nuclei, and numerous mitoses. Enlarged or even giant cells with multiple nuclei are focally located, along with coagulative necrotic loci and regions of severe anaplasia (Figures 3 and 4).

Immune-histochemical study was performed and revealed cells positive for SMA (Figure 5) and for

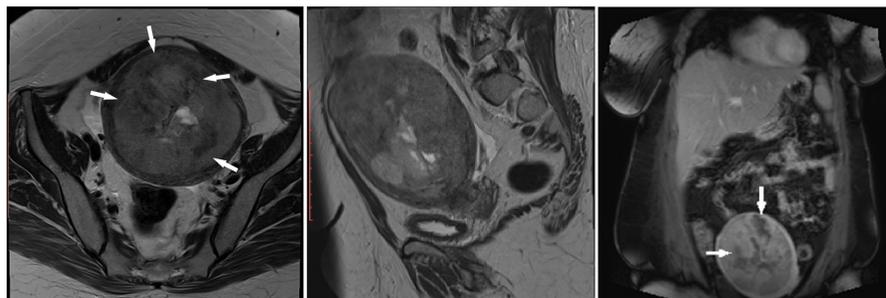


FIGURE 1 Intrauterine non-homogenous mass detected in the MRI scan.

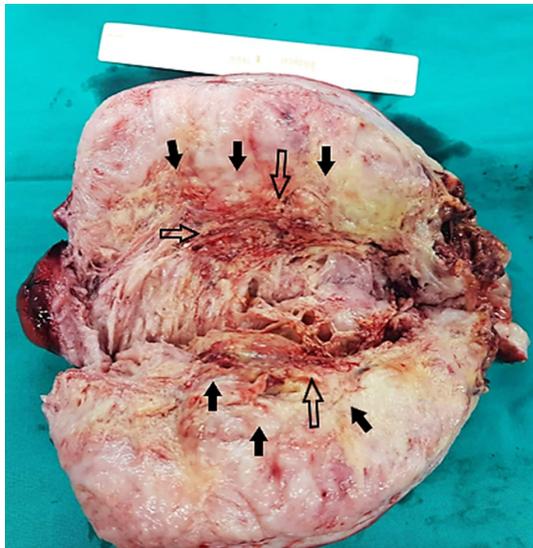


FIGURE 2 Leiomyosarcoma was shown to be soft and large relative to the total uterine volume, with irregular borders noted to be invading the myometrium (block arrows) with a hemorrhagic center (line arrow). The ruler next to the uterus measures 15 cm.

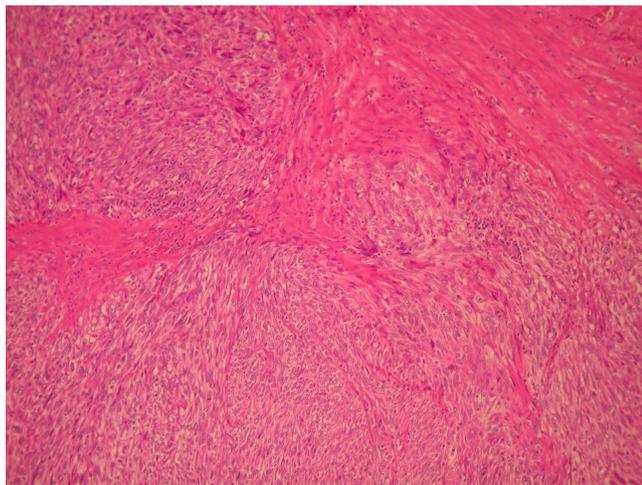


FIGURE 3 High-grade leiomyosarcoma which invades the myometrium (hematoxylin & eosin, $\times 100$).

h-caldesmon (Figure 6), with desmin, keratin AE1, and AE3 positivity being observed only focally. Focally, few to many cells possessing mainly severe anaplastic features, were positive for β -hCG expression (Figures 7 and 8), thus definitively confirming our initial hypothesis that the leiomyosarcoma was the source of the elevated serum β -hCG. No lymph node metastases were observed, and the cytology examination of the peritoneal washings was negative.

3 | DISCUSSION

It is indisputable that the most probable scenario of a positive urine pregnancy test in reproductive age is ongoing

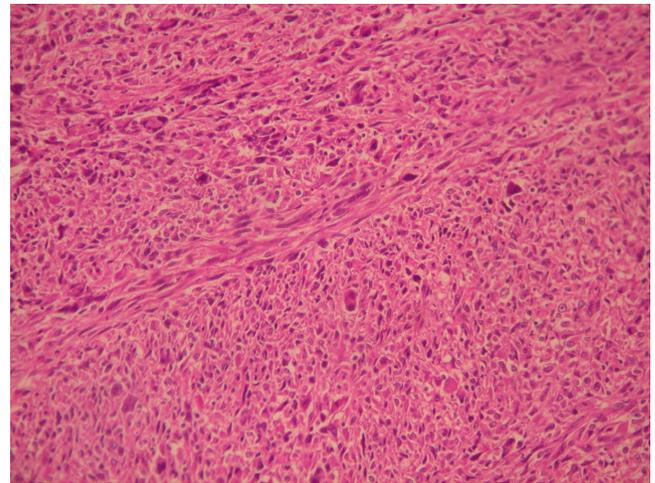


FIGURE 4 Typical histological characteristics of a high-grade leiomyosarcoma (hematoxylin & eosin, $\times 200$).

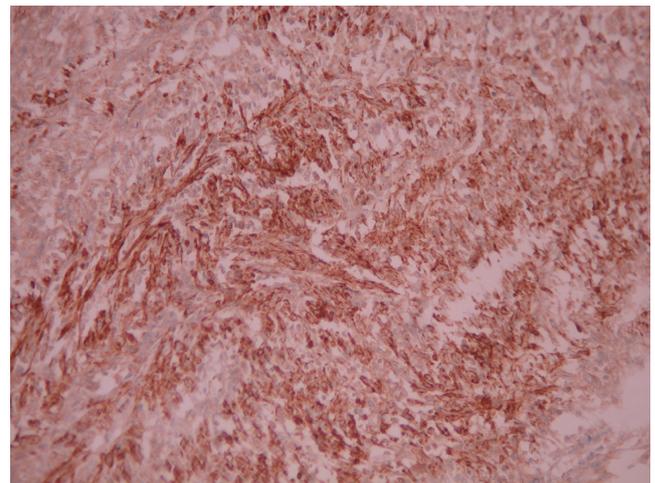


FIGURE 5 Immuno-histochemical study showed cells positive for SMA staining ($\times 200$).

pregnancy. This being the case, the differential diagnosis of elevated serum β -hCG can be quite challenging in cases where hormone-producing tumors are present.¹⁰ In our case, pregnancy was ruled out due to the patient's post-menopausal status. Such tumors are mainly trophoblastic tumors, especially choriocarcinoma and germ-cell neoplasia, as well as tumors of the breast, lung, bladder, prostate, large intestine, liver, kidney, and pancreas.^{11,12} These elevated levels of serum β -hCG have been hypothesized to act as an autocrine growth factor inhibiting apoptosis and thus facilitating tumor proliferation.¹³

However, there has been a limited number of cases of β -hCG-producing sarcomas, even fewer leiomyosarcomas in particular, documented in the available literature. In 1986, Meredith et al.¹⁰ first presented a case of intestinal leiomyosarcoma in a 22-year-old woman with a history of lung metastases. Following resection, β -hCG levels were elevated (7550 mIU/ml 20 days post-op), and

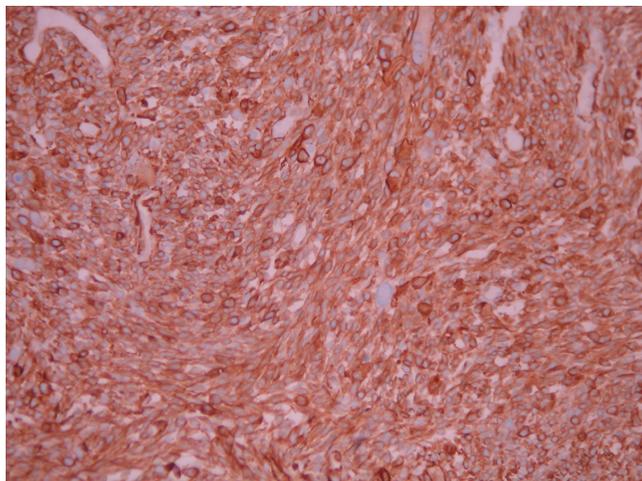


FIGURE 6 Immunohistochemical study showed positivity for the h-caldesmon immunostain ($\times 200$).

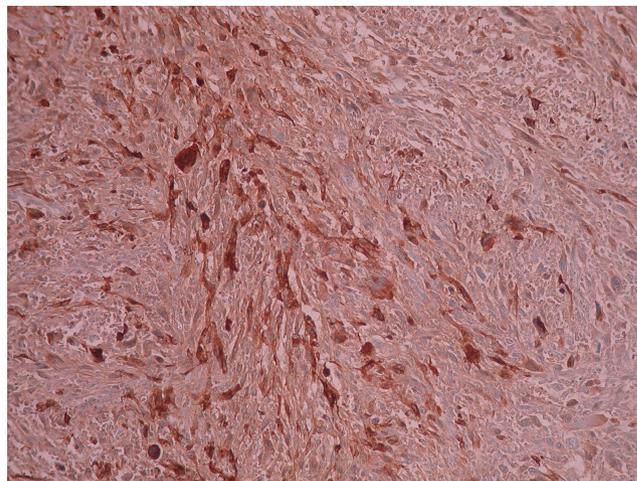


FIGURE 8 Focal positivity of a few cells for β -hCG after immune-histochemical examination ($\times 200$).

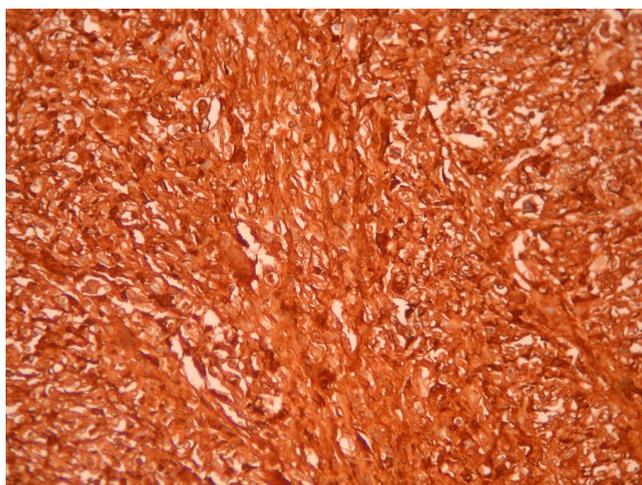


FIGURE 7 Focal positivity of numerous neoplastic cells for β -hCG after immune-histochemical examination ($\times 200$).

more pelvic masses were discovered, with the patient perishing 6 weeks later. Russel et al.¹⁴ documented the case of a 67-year-old female presenting with abdominal pain caused by a retroperitoneal liposarcoma, largely dedifferentiated with leiomyosarcomatous elements. Serum β -hCG levels were significantly elevated (210.3 mIU/ml) and further increased 26 days after surgery (1046 mIU/ml). Shortly thereafter, several liver metastases were uncovered and the patient died 2 months later.

In this report, we presented a case of uterine leiomyosarcoma. These tumors in general are rare malignancies, comprising 1% of all uterine carcinomas, and are most frequently diagnosed in menopausal women with a history of uterine fibroids, usually during histologic analysis post-myomectomy.¹⁵ Incidence rates range from 0.4–0.6 per 100,000,^{15,16} and early-stage disease (FIGO Stages I and II) is diagnosed in approximately 70–87% of cases,^{15,17} with

tumors arising in pre-menopausal women developing more aggressively (early-stage disease 45%).¹⁸ 5-year survival rate has been documented to be approximately 50% in earlier stages, compared to 90% of most gynecologic cancers,^{15,19} and drops dramatically at more advanced stages and when more aggressive histopathologic characteristics are present.^{17,19}

With regard to β -hCG-producing uterine leiomyosarcomas, only 2 prior cases have ever been reported in the available literature. Liang et al.⁶ were the first to document the case of a 49-year-old woman with abnormal uterine bleeding persisting for months and a history of uterine fibroids, who on examination had elevated β -hCG levels, an advanced, spindle cell uterine leiomyosarcoma, and extensive peritoneal metastases in subsequent weeks. Krishnan et al.²⁰ documented a 33-year-old woman with a four-month history of vaginal bleeding and elevated β -hCG (49.7 IU/L at presentation and 90.1 IU/L prior to surgery), caused by pleomorphic, undifferentiated, high-grade sarcoma. After surgery, serum β -hCG levels dropped to 0.9 IU/L post-op and to 1.1 IU/L at 3-month follow-up. At a 6-month follow-up, multiple lung metastases were discovered and adjuvant chemotherapy was planned.

To our knowledge, the case reported here is the third ever published case of β -hCG-producing leiomyosarcoma located in the uterus. The emergence of such cases raises questions regarding the possible application of β -hCG as a diagnostic or a prognostic biomarker. Due to the limited number of studies and cases, only empirical evidence is available. The majority of available case reports as well as a case series study²¹ hypothesize that there could be a correlation between β -hCG secretion and a more adverse outcome, since most of these tumors are more aggressive.^{6,20} This is consistent with our findings as well, given the presence of multiple distant metastases and the loco-regional

extent of the disease. However, there are reported cases and a different case series²² where β -hCG production was not associated with advanced disease and conclude that it is not a predictor of the sarcoma's biological behavior.^{8,23} With regard to uterine leiomyosarcomas that secrete β -hCG, all three cases developed distant metastases; thus, the association with a more adverse outcome is consistent, but as mentioned above, just empirical. The application of β -hCG as a prognostic biomarker is inconsistent as well, with the levels in some cases persisting or further increasing post-operatively whereas in others, dropping after, thus not always accurately reflecting the underlying pathology. This was observed in our case as well, with β -hCG levels dropping, despite our initial hypothesis of the opposite due to the lung metastases.

4 | CONCLUSION

Uterine leiomyosarcoma is an aggressive and frequently lethal neoplasia, with a vital prognostic factor being the extent of the disease. We presented the particularly rare case of a β -hCG-producing uterine leiomyosarcoma, in which β -hCG itself may constitute a prognostic factor of a more adverse outcome with the disease metastasizing in distant loci. However, this is not always consistent and due to the small number of available documented cases, a correlation cannot be definitively proven. Further studies and reports of similar cases are needed to provide further insight on this extremely scarce pathology and ascertain the validity of this correlation.

AUTHOR CONTRIBUTIONS

Elias Tsakos was involved in conception and design, administrative support, provision of study materials or patients, patient care, collection and assembly of data, manuscript writing and final approval of the manuscript. Emmanouil M. Xydias was involved in conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of the manuscript. Apostolos C. Ziogas was involved in conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of the manuscript. Kanelina Bimpa was involved in conception and design, administrative support, data analysis and interpretation, patient care, manuscript writing and final approval of the manuscript. Angelos Sioutas was involved in conception and design, provision of study materials or patients, patient care, collection and assembly of data, data analysis and interpretation and final approval of the manuscript. Katerina Zarampouka was involved in data analysis and interpretation, provision of study materials, histologic assessment of tumor samples,

manuscript writing and final approval of the manuscript. Georgios Tampakoudis was involved in conception and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation and final approval of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

The patient provided informed written consent for publication, which was later re-affirmed by her closest relatives, postmortem.

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