Case Report

Misdiagnosis of leiomyosarcomas: case report and medico-legal issues

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Background: The perception of a delay or misdiagnosis of cancers is associated with significant numbers of malpractice claims with an increase of cost of the national healthcare system. Uterine leiomyosarcoma is a rare uterine malignancy, it accounts for 1–2% of uterine malignancies. Preoperative diagnosis of uterine sarcomas can be difficult, in some case almost impossible. The symptoms can be vague and nonspecific (lower abdominal, pelvic pain, abdominal distension, abnormal vaginal bleeding) and can resemble those of more common leiomyoma.

Case Description: We present a case of misdiagnosis of leiomyosarcomas. A 32-year-old woman underwent a transvaginal sonography by a general gynaecologist as routine check-up, the patient presented regular menses and was asymptomatic and her past medical and gynaecologic history was unremarkable. The sonography showed a solid subserosa-intramural uterine mass and the uterine lesion was diagnosed as leiomyoma and it has been treated consequently. A sonography 60 months from diagnosis revealed an increase of 1.6 cm in the maximum diameter of the uterine mass and the intra-lesion hypoechoic area reached 4.2×3.4 cm in diameter. Due to the increase of the uterine mass the patient underwent laparoscopic myomectomy. During surgery some fragments were sent to pathologist and diagnosis was "malignant neoplasm with high mitotic index". Due to frozen section results the surgeons opted for open surgery with total hysterectomy with preservation of fallopian tubes and ovaries postoperative pathological examination revealed high grade uterine leiomyosarcoma, stage I. The disease was rapidly progressive and the patient died of disease 13 months after surgery. On the assumption that death occurred because of diagnostic delay, patient's relatives decided to instigate a legal action under criminal law and civil law and medical doctors were sued for delayed diagnosis and inappropriate treatment; the case was discussed in regional court and after thorough discussion, no professional liability was found.

Conclusions: Our paper is interesting because we analyze the case of misdiagnosis from a medico-legal perspective highlighting the importance of using evidence-based guidelines in clinical practice and of an accurate preoperative informed consent as a fundamental issue to limit medico-legal responsibility.

Keywords: Leiomyosarcoma; uterine sarcoma; medical liability; morcellation; case report

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Introduction

The perception of a delay or misdiagnosis of cancers is associated with significant numbers of malpractice claims (1,2). It is also a source of distress for physician, relatives, and an increase of cost as well as a relevant economic impact to the National Health Service (3).

Here we report a case of misdiagnosis of leiomyosarcoma in a 32-year-old woman. The uterine lesion was diagnosed as leiomyoma and it has been treated consequently. On the assumption that death occurred because of diagnostic delay, patient's relatives decided to instigate a legal action under criminal law and civil law. We analyze case of misdiagnosis from a medico-legal perspective.

Uterine sarcoma are rare tumors that account for approximately 1% of female genital tract malignancies and 3% to 7% of uterine cancers (4). Among them, uterine leiomyosarcoma represents the most common type of uterine sarcomas (60–70%) and is associated with poor prognosis (5,6). Most patients with uterine sarcomas are postmenopausal (7). Sarcomas must be differentiated from uterine myomas which are the benign counterpart particularly frequent in young women; in fact, myomas affect approximately 70% of the female population between ages 40 and 50 years (8). The distinction between these two entities is difficult and is based on histology (9). Preoperatively differential diagnosis can be difficult because symptoms and signs of both tumors are similar (10).

Currently, preoperative work-up does not reliably distinguish between benign leiomyomas and sarcomas and diagnosis is often made on histology after surgery for presumed benign disease; therefore, inappropriate surgical procedures such as morcellation and delayed surgery can worsen the prognosis of the patient (11).

We present the following case in accordance with the CARE reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-20-66/rc).

Case presentation

A 32-year-old woman underwent a transvaginal sonography by a general gynaecologist as routine check-up. The sonography showed a solid subserosa-intramural uterine mass, diagnosed as myoma of the anterior wall of the uterus, of 3.5×4.2×4.6 cm in diameter. Her past medical and gynaecologic history was unremarkable. The patient presented regular menses and was asymptomatic. During the subsequent 36-month follow-up the myoma increased less than 1 cm in maximum diameter at sonography. At 48-month sonography a different hypoechoic area of 1.4×1.5 cm diameter was identified inside the uterine mass (identified as a second myoma). A sonography 60 months from diagnosis revealed an increase of 1.6 cm in the maximum diameter of the uterine mass and the intra-lesion hypoechoic area reached 4.2×3.4 cm in diameter.

The woman was referred to a tertiary care centre; a transvaginal sonography revealed a myometrial node 6.9 ×6.2 cm in diameter with a 4.5 cm anechoic necrotic area; the patient was still asymptomatic. Because of this, the patient was recommended laparoscopic myomectomy; the patient was put on the wait list and, 6 months after, a preoperative sonography showed an increase of the lesion (9 cm in maximum diameter), and she underwent surgery.

During minimally invasive surgery, the nodule was identified on the anterior uterine wall and the overlying myometrium was incised. A considerable amount of cerebroid material emerged from the incision raising the suspicion of malignant neoplasm. Some fragments were sent to pathologist for frozen section and diagnosis was "malignant neoplasm with high mitotic index". Then, due to technical difficulties and frozen section results the surgeons opted for open surgery. The surgery was completed with total hysterectomy with preservation of fallopian tubes and ovaries. Surgical exploration of the abdomen revealed no further disease sites. A histopathological examination revealed "*number of mitosis 136/50HPF. Atypical mitosis, severe cytological atypia. gigantocellular and syncytial component and tumor necrosis*". *(Figures 1-3)*. Definitive histology was high grade uterine leiomyosarcoma, stage I. A subsequent tomography was negative for metastasis.

The patient underwent chemotherapy and external radiotherapy. PET scan at the end of the treatments showed multiple abdominal, pelvic, and pulmonary metastases. The disease was rapidly progressive, the patient died of disease 13 months after surgery.

Medical doctors were sued for delayed diagnosis and inappropriate treatment; the case was discussed in regional court and after thorough discussion, no professional liability was found.

The study was performed in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Patient identification remained anonymous and informed consent was waived due to the observational nature of the study.

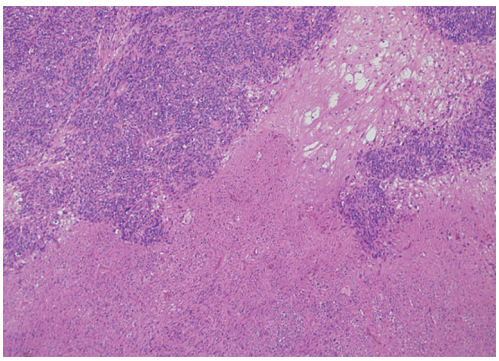

Figure 1 Leiomyosarcoma. Interface between tumor and necrosis (H&E 20×).

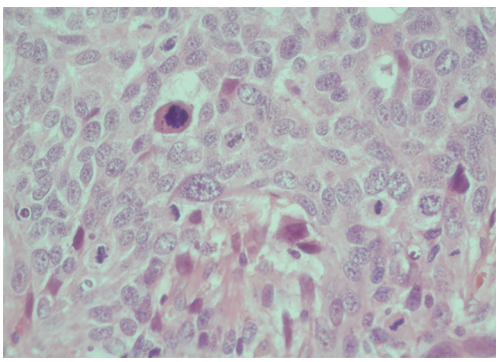

Figure 2 High mitotic activity, with an atypical mitosis (H&E 40×).

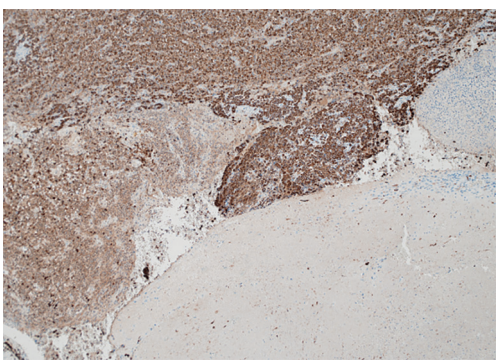

Figure 3 Antibody anti-desmin is diffusely positive in the neoplastic component (IHC 20×).

Discussion

Difficult preoperative diagnosis of leiomyosarcoma can lead to delay of treatment and inadequate surgery, as morcellation of the neoplasia. The current case represents the "classic" legal litigation derived from these features of the disease.

For Italian legal system, the burden of proof lies with the defendant and the clinicians or hospital must prove to have acted diligently and have fulfilled their contractual obligation (12). Regarding to omissive conduct (cases of missed diagnosis), the chain of causation between the omission and its subsequent effects is configurable only if the necessary action had been taken and the event would not have taken place with a high degree of rational credibility, or it would have taken place later, or with less detrimental intensity (3).

Here we report and discuss the results of medico-legal consultancy. A question was related to the clinical approaches adopted in the presence of a uterine fibroid in a young and asymptomatic woman. Another issue was the choice of treatment related to the volume of the myoma. "Was the management of myoma consistent with good clinical practice?" was the question posed by the judge.

The first finding of a myoma was when the patient was 32 years old, during a follow-up visit and the gynaecologist recommended a "wait and see" approach. Myomas can be variably treated; the management can be abstentionist, medical and surgical or combined; it depends on symptoms, size and location of fibroids, age of the patient, parity and desire of pregnancy (13).

In the present case, there were no complaints in the choice not to proceed surgically in a young woman, affected by a single myomatous node of 3.5×4.2×4.6 cm, almost asymptomatic, eager for offspring. Expectant management with observation is increasingly recognized as a reasonable management and surgery can negatively interfere with the patient's reproductive potential. Generally, myoma of 5 cm or more in diameter is considered susceptible to surgery; other sources suggest surgery when the myoma is at least 8 cm in diameter, or when the uterus reaches a volume corresponding to that of a pregnancy at 12 weeks (14).

Other factors that affect management choices include the patient's age, patient's desire to become pregnant, the surgical procedure to be adopted and the awareness that surgery on large uterus is burdened by a greater risk of transfusion and complications.

Uterine leiomyosarcoma is a rare uterine malignancy, it accounts for 1–2% of uterine malignancies. Preoperative diagnosis of uterine sarcomas can be difficult, in some case almost impossible. The symptoms can be vague and nonspecific (lower abdominal, pelvic pain, abdominal distension, abnormal vaginal bleeding) and can resemble those of more common leiomyoma (15). Some clinical features, as abnormal uterine bleeding in post-menopause, rapid growth of the lesion and advanced age, are to be considered for sign of uterine sarcoma, but their predictive value is not sufficient for diagnosis (16). For this reason, it is prudent to value any suspicion and consider a rapid growth as a possible sign of malignancy (17).

On these premises, it is evident that the "wait and see" strategy was correct until the sonography showed stable dimensions of the myoma but revealed in its context "another small nodule of myoma of 1.4×1.5 cm".

It is known that uterine fibroids can develop adjacent to each other, while there is no knowledge that a second one can grow inside a myomatous node. With an *ex post* evaluation, it seems reasonable to think that the area defined as the second myomatous node was a colliquation area or anyway a newly appeared feature of the mass.

Differential ultrasound diagnostics with sarcomas is very difficult and imprecise and does not offer pathognomonic framework for uterine sarcoma (18,19). In the past years, a few studies have described the sonographic appearance of uterine sarcomas, suggesting specific features such as large solid lesions with heterogeneous echogenicity, irregular cystic areas, irregular margins, rich vascularization, "unstructured" solid tissue in the absence of shadow cones and calcification (20,21). Nevertheless, these sonographic criteria do not warrant a predictive performance of the imaging modality. Magnetic resonance imaging represents the best approach to imaging of uterine sarcoma, but even though some features suggestive of disease have been described, no definitive imaging findings differentiate leiomyoma from sarcomas (22).

In a young and asymptomatic woman, the debate prompted that no different strategy should have been prospected, so no malpractice was attributable to the gynecologist at this time point of the events.

The transvaginal sonography performed 12 months after diagnosis reported a sudden increase in the volumetric growth: dimensions of the large nodule were 6.6×5.6 cm with a 2.5 cm increase in the maximum diameter and the presumed second myoma was 4.2×3.4 cm large, with almost a threefold increase in maximum diameter. The woman was correctly referred to a tertiary centre where, after sonography result, surgical indication for laparoscopic myomectomy was assessed.

About this aspect, it was also requested to medical expert to evaluate if the laparoscopic technique was adequate to remove a myoma of 9 cm in diameter. "Was the operating technique consistent with good practice?"

The medico-legal evaluation stated that the laparoscopic approach was correct when a single intramural myoma is present, like in the present case, so gynecologist's responsibility was not engaged. As far as fibroid volume for selecting laparoscopic surgery, there is no boundary limit but the indication for the laparoscopic route depends on expertise of the surgeon. Various reports warrant that abdominal hysterectomy or myomectomy reduce the chance of spreading cancer cells in women with undiagnosed uterine sarcomas, but this aggressive approach is associated with increased morbidity (23,24)

The incidence of leiomyosarcomas in women submitted to surgery for presumed uterine fibroids is not clearly assessed; it was considered about 0.5% (25), but a recent meta-analysis reported a much smaller frequency, ranging from 0.12 to 0.51 per 1,000 procedures (26).

Considering the rarity of the disease and the burden of morbidity on large series of patients, the Royal College of Obstetricians and Gynaecologists, as well the American College of Obstetricians and Gynecologists recommend that the patient should be engaged in a shared decision-making, explaining risks and benefits of each approach to surgery for presumed leiomyomas.

In the present case, after myometrial incision and tumor appearance on the uterine scar, the procedure was aborted; no laparoscopic morcellation was performed and laparoscopy was converted in laparotomy. According to several studies (27), laparoscopic morcellation should not be used in case of leiomyosarcoma due to the risks of dissemination of cancer cells and the risk of reducing the chances of survival (28). Laparoscopic morcellation consists of reduction of the myoma in small fragments that can be extracted from the abdominal cavity through the 10-mm diameter trocars; the procedure is obtained with devices consisting of a rotating blade that slices up the tissue and this procedure is indeed associated to some cells

spreading in the abdomen. The use of morcellation is also related to development of Leiomyomatosis Peritonealis Disseminata. LPD is a rare benign disease characterized by the presence of multiple smooth muscle nodules throughout the peritoneal cavity and can occur many years after the procedure. During the electrical morcellation, in fact, pieces of the sample are dispersed throughout the abdominal cavity where they implant in normal tissue and give rise to the development of fibrotic nodules (29). In case of neoplastic myometrial nodules, another possibility of freeing tissue cells in the pelvis is to fragment the lesion during hysteroscopic surgery, vaginal surgery and even during laparotomic procedures when the integrity of the neoplastic mass is damaged. In the case here reported the incision of the myometrial tissue surrounding the leiomyosarcoma has led to the spread of cancer cells. The result was unexpected because the surgeons had mis-interpreted the uterine disease as benign. Here again the medico-legal assessment did not find any responsibility due to the difficulty to obtain a correct pre-operative diagnosis.

Another point to be evaluated was that, after the results of frozen section, the surgeon removed the uterus, leaving ovaries and tubes. The standard surgical treatment of leiomyosarcoma is hysterectomy with bilateral salpingo-oophorectomy; however, in young and pre-menopausal patients it is reasonable to preserve the ovaries, as the survival is not hampered by the ovarian-sparing procedure (17). In pre-menopausal patients, the problem of preservation of the ovaries must be carefully considered since their involvement is found in only 3% of cases. A study carried out at the Mayo Clinic examines 240 cases of leiomyosarcoma and evaluates a group of patients in which the ovaries were preserved at the time of hysterectomy. No significant difference was observed between patients with preserved ovaries and with removed ovaries in terms of disease-free survival and overall survival (30).

Finally, the plaintiff complained because of six-month interval between indication and surgery. The judge asked his medical expert whether a six-month anticipation of the surgical procedure would had changed the patient's prognosis. Leiomyosarcomas are very aggressive tumors associated with poor prognosis (4). Among the prognostic factors of this type of tumor, the Stage is certainly fundamental for sarcomas but another decisive element is the size of the tumor and the FIGO classification differentiates, for stage I, two subgroups according to whether the tumor is less or more 5 cm in diameter. Another fundamental parameter is the mitotic index, the extent of cytological atypia and the presence of coagulating necrosis. To these must be added the age of the patient considering that the prognosis is better for premenopausal patients.

When the patient was referred to the tertiary centre the uterine mass, considered a leiomyoma at sonography, was 66 mm in maximum diameter. At this moment the leiomyosarcoma had, therefore, already all the negative prognostic factor currently recognized in the statistical analysis of survival, i.e., dimensions above 5 cm in diameter, very high mitotic index (this was verified retrospectively by the 3-cm volumetric growth rate in the pre-operative period), cellular anaplasia (indirectly demonstrated by the growth rate of the tumor), tumor necrosis (observed as anechoic areas at ultrasound scans). No prognostic parameter would have been favourably influenced by a surgical anticipation. It is therefore not possible to affirm that the outcome in terms of survival would have been changed in case of anticipation of surgery.

Conclusions

The medical expert of the judge, in his medico-legal report, concluded that the preoperative diagnosis of uterine sarcoma in Stage I was not possible, especially in an asymptomatic patient so the judges acquitted the physician sustaining that he had acted properly, in full compliance with the medical duty of care to the patient. Despite the fact that the physician did not make a diagnosis of leiomyosarcoma, prior to surgery, it was not possible to assess any professional liability.

The judges stated that the case was conducted in accordance with guidelines for good clinical practice and following the appropriate standard of care imposed by the law. No different course of actions could have decreased the chance of death.

Our paper highlights the importance to use evidence-based guidelines in clinical practice as a fundamental issue to limit medico-legal responsibility.

A preoperative informed consent with clear and accurate information about treatment options and their associated risks should be provided to women with presumed uterine fibroids. Patients should be informed that-although rarely -unexpected uterine sarcoma can be found during surgery; they should be aware that there is no reliable preoperative diagnostic test to diagnose a sarcoma and early diagnosis is often impossible. Furthermore, information about the risk of using laparoscopic morcellators should be provided to

the patient.

Improving doctor-patient relationship, consisting in an appropriate counselling or better in a real shared decision making prior to surgery may decrease the number of lawsuits, considering that miscommunication is one of the main reasons of medical claims after an adverse outcome.

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Footnote

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