Endometrial stromal sarcoma in a 27-year-old woman. Case report and literature review

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Abstract

Endometrial stromal tumors are very rare, representing approximately 0.2% of uterine malignancies, having an incidence of one to two from a million of women. The diagnosis cannot be established by imaging, it is histopathological only, often necessitate supplementary immunohistochemistry tests. We report the case of a 27-year-old woman who had an initial diagnosis, in another hospital, of uterine adenomyoma, established by dilatation and uterine curettage and then by subsequently histopathological exam. This diagnosis led to an initial non-oncological surgery, with interannexial total hysterectomy. The establishment of the final histopathological diagnosis of stromal endometrial sarcoma has led to a serious reassessment of the case. Making a review of the literature, we found very few cases of endometrial stromal sarcoma in young women less than 30 years old and we have not identified any clear strategy of treatment. However, from precautionary and considering that may be at risk, even with very few cases reported, the distance metastases can be present, sometimes at large intervals of time, we decided, for oncological safety, reintervention after one month. At the second surgery, it was practiced bilateral salpingo-ovarectomy, cardinal ligaments excision, partial omentectomy, bilateral pelvic lymphadenectomy extended lumbo-aortic and interaorto-cava, sampling biopsy from the inguinal femoral adenopathy and re-excision of the vaginal vault. The evolution was favorable, the patient being follow-up together with the oncologist specialist.

Keywords: endometrial stromal sarcoma, uterus sarcoma, immunohistochemistry.

Introduction

Endometrial stromal sarcomas (ESS) are malignant tumors with very low incidence, representing around 10% of uterine sarcomas [1, 2]. Uterine mesenchymal tumors come from the uterus mesenchyme, which consists of endometrial stroma, smooth muscle and blood vessels or a combination of these [3]. Uterine mesenchymal tumors affect more black women than white and the most frequent are leiomyosarcomas and endometrial stromal tumors [4]. The most common signs and symptoms are abnormal uterine bleeding, increase in size of the uterus and pelvic pain. For a better perspective, non-invasive imaging, such as ultrasound (US) and magnetic resonance imaging (MRI) can be used. Radiologists should be alarmed when the appearance of an is extensive, heterogeneous mass with an irregular contour, as it suggests the presence of sarcoma [5]. Uterine sarcomas have been classified into three histological groups: malignant mixed Müllerian tumor (MMMT), leiomyosarcoma (LMS) and ESS [6]. The World Health Organization (WHO) has classified endometrial stromal tumor into benign endometrial stromal nodule (ESN) and ESS. ESS can be low-grade and high-grade tumors. Classification is made by cell morphology and mitotic count. [7]. The prognosis of these tumors following surgery varies, with ESS benefiting of a better prognosis compared to leiomyosarcoma or undifferentiated endometrial sarcoma [4]. Low-grade ESS usually occurs in young women (mean age 39 years) and high-grade ESS occurs in older women (mean age 61 years).

The aim of this case report is to draw attention to this rare but severe diagnosis. Our case was interesting for three reasons: the very young age of the patient and the fact that, although we lost quite a long time (over a year) through confusion with uterine adenomyoma, from the oncological point of view, the local or distant dissemination has not existed in this case of low-grade ESS. The third reason was represented by the need to establish a strategy for treatment even in the absence of large trials or studies on this topic.
**Case presentation**

A 27-year-old woman, C.R., was admitted on January 2017 in Department of Obstetrics and Gynecology, “St. Pantelimon” Emergency Clinical Hospital, Bucharest, Romania, for moderate, persistent, vaginal bleeding and pelvic diffuse pain in order to establish therapeutic specialist conduct. In the patient’s personal history, we noted that she has one vaginal birth in 2008 and one miscarriage. She is non-smoker and with no history of contraceptive use, with irregular and abundant menstrual cycle about two years without other significant diseases and without important medical family history. However, in a previous clinical and US examinations, performed in another medical unit, the diagnosis of uterine adenomyoma was established. A dilation and uterine curettage was performed in March 2016. Histopathological microscopic examination shows the need for a differential diagnosis between benign ESN and atypical polypoid adenomyoma and recommends additional immunohistochemical tests. The final diagnosis of our colleagues was uterine adenomyoma, so the initial therapeutic management was appropriate for that diagnosis. At the admission in our Department, the patient was cooperative, with pale skin, blood pressure 110/60 mmHg, pulse 72 beats/min, with moderate vaginal bleeding. The gynecological examination with speculum identify a polypoid tumor formation about 5/3 cm, with bleeding, apparently looking for a necrotic uterine fibroid prolapse through the cervix into the vagina. On the pelvic bimanual examination, the uterus was firm, with increased volume and preserved mobility, causing mild pain on palpation. Bilateral adnexa were normal. After completing the laboratory exams with blood tests within hemoglobin 9.72 g/dL, hematocrit 31.2% and other blood exams in normal range, an abdominal and transvaginal US examination was performed. US images were also suggested for the diagnosis of uterine polyfibromatosis with a cervical well-defined mass.

Computed tomography (CT) with contrast substance identifies increased uterus with the dimensions of 8/7/5 cm, irregular contour and with intense inhomogeneous structure by presence of a multinodular tumor formation, at the uterine fundic level. The largest node has 3 cm and the entire tumor has a local intramyometrial invasive character until uterine peritoneum and expansive through the cervix into the vagina (Figure 1). There also appear a cleavage plan between the uterus and the bladder, sigmoid colon and rectum, with no pelvic adenopaties and no ascites liquid.

![Figure 1 – CT scan demonstrating a macronodular, invasive, tumor mass, at the uterine fundus level, expansive through the cervix into the vagina.](image1)

After obtained informed consent, exploratory surgery through laparotomy was performed under general anesthesia and followed by interannexial total hysterectomy, taking into account the patient’s age, macroscopic normal appearance of ovaries and Fallopian tubes and previously established pathological diagnostic (Figure 2).

Evolution after surgery was without any complication. On day 4, the patient was discharged with a good general condition, afebrile.

Although, the final histopathology diagnostic describes malignant tumor infiltration of the uterine wall consisting of round cells or oval to spindle-shaped cells with low and eosinophilic cytoplasm, oval and basophil nuclei, arranged in islands with expansive growth pattern, rare atypical mitoses and frequent arterial type vessels (Figures 3 and 4), so different from the initial pathological diagnostic.

![Figure 2 – Macroscopic section of the uterus: poly-nodular, invasive mass at the uterine fundus.](image2)

![Figure 3 – Low-grade endometrial stromal sarcoma: tumor cells disposed in a whorled pattern around arteriole-type vessels. HE staining, ×100.](image3)
Endometrial stromal sarcoma in a 27-year-old woman. Case report and literature review

Figure 4 – Low-grade endometrial stromal sarcoma: highly cellular proliferation of uniform, oval to spindle cells with scant cytoplasm. HE staining, ×200.

Immunohistochemistry (IHC) examination shows CD10 (common acute lymphoblastic leukemia antigen – CALLA, nephrilysin, enkephalinase) positive focally in tumor cells. Immunolocalization of CD10 was performed using a peroxidase EnVision kit (Dako, Ely, UK, 1/100 dilution). CD10 is a cell surface glycoprotein present on endometrial stromal cells and endothelial cells. Some studies have shown that CD10 is a sensitive marker for endometrial stromal neoplasms, especially ESN and low-grade ESS.

It has also been observed alpha-smooth muscle actin (α-SMA, clone 1A4, mouse monoclonal, Sigma, 1/1000 dilution). Actins are globular multi-functional proteins that form microfilaments. In our case, α-SMA was positive in myometrium and vessels. Estrogen receptor (ER) was positive in about 98% of tumor cells (Figure 5). ERs are steroid nuclear receptors. Tumors that have in a large percentage ERs and progesterone receptors (PRs) react positively to antiestrogen therapy. For highlighting ER, we used anti-ER antibody, clone SP1, rabbit anti-human, Lab Vision, 1/200 dilution and for PR, anti-PR antibody, clone rabbit anti-human, Dako, 1/100 dilution, with IHC Tek antibody diluent. Ki67, a strong marker for proliferative activity, was positive (Figure 6) in about 15% of tumor cells (anti-Ki67 antibody, clone MIB5, mouse anti-rat, Dako, 1/100 dilution). MNF116, a very important marker of epithelial differentiation, was negative (anti-cytokeratin antibody, clone MNF116, mouse anti-human, Dako, 1/200 dilution). p53 was also negative (anti-p53 antibody, clone mouse anti-rat, Cymbus Biotechnology, 1/100 dilution). Tumor suppressor p53 regulates the mechanisms that prevent cancer and has an important role in apoptosis (programmed cell death), genome stability and growth of blood vessels. PR was positive in 98% of tumor cells (Figure 7).

Figure 5 – Low-grade endometrial stromal sarcoma. The tumor cells show diffuse positivity for ER. Anti-ER antibody immunostaining, ×200. ER: Estrogen receptor.

Figure 6 – Low-grade endometrial stromal sarcoma. Ki67 was positive in 15% of the tumor cells nuclei showing proliferative activity. Anti-Ki67 antibody immunostaining, ×200.

Figure 7 – Low-grade endometrial stromal sarcoma. PR is intensely positive in tumor cells nuclei. Anti-PR antibody immunostaining, ×200. PR: Progesterone receptor.

Surprisingly, final diagnosis was low-grade ESS. However, considering that may be a risk for disseminated disease for the patient, even very small statistically, of distance metastases, sometimes at large intervals of time, we decided after informed consent of the patient, for oncological safety, reoperation, after one-month interval. At the second surgery, it was practiced, under general anesthesia, bilateral salpingo-ovarectomy, cardinal liga-
ments excision, partial omentectomy, bilateral pelvic lymphadenectomy extended lumbo-aortic and interaortico-cava, sampling biopsy from the inguinal femoral adenopathy and re-excision of the vaginal vault. Fortunately, all the anatomical elements have been extirpated without tumor infiltration and all lymph nodes were negative (28 paraffin blocks). Postoperative stage, according with International Federation of Gynecology and Obstetrics (FIGO) and American Joint Committee on Cancer (AJCC) staging systems, was IB (T1B, N0, M0). The evolution was favorable, the patient being follow-up with help of the oncologist doctor. Two questions have appeared in the follow-up: If we were too extensive from the point of view of surgical intervention and if the patient, at this young age, needs hormone replacement therapy after bilateral oophorectomy? After surgery, evolution of the patient was without any complication and she was discharged in the fifth day.

§ Discussions

Sarcomas of the uterus are an infrequent form of malignancy, presenting in about 2–5% of all patients with uterine malignancy and having an incidence of approximately 1–2/100 000 women in the general population [4]. ESS are extremely rare; they represent about 10% of all uterine sarcomas and nearly 0.2% of all uterine malignancies [5]. Annually, the incidence of ESS is 1–2/1 000 000 women [5]. It is diagnosed in younger women and the average age is between 42 to 58 years old, 10% to 25% are premenopausal [4]. ESS are mesenchymal tumors and they were separated into low-grade endometrial sarcomas, ESN and high-grade endometrial sarcomas based on mitotic count. Recently, because of the absence of differentiation or histological similarity to the endometrial stroma, high-grade endometrial sarcomas were renamed as undifferentiated endometrial/uterine sarcomas. Differentiation between the two classes is not made on mitotic basis, but on particularities such as nuclear pleomorphism and necrosis [1, 2].

There is little data about stromal sarcomas origin and biology. The pathogenesis of ESS is unknown, but exposure to radiations, Tamoxifen and conditions such as polycystic disease of ovary are implicated [8]. Some studies shown that in leiomyosarcomas and also in endometrial sarcomas are frequent mutations in tumor protein p53 (TP53), alpha thalassemia/mental retardation syndrome X-linked (ATRX) and mediator complex subunit 12 (MED12) genes [9]. Chromosomal aberrations and endometrial sarcomas are connected. Chromosomal deletion on 7p was the most frequent finding (55.6%) and it may be involved in tumor progress [10]. Is very difficult to differentiate ESS from the normal endometrium on curettage fragments and the definitive diagnosis can be made only by histopathological exam and IHC tests after hysterectomy [11]. Low-grade ESS is, generally, a clinical indolent tumor. It has a plexiform vascularization, cytological atypia is minimal and mitotic figures are not frequent [3, 4]. Local setbacks and metastasis at distance can take place even 20 years after initial diagnosis [5]. High-grade ESS (recently renamed as undifferentiated endometrial uterine sarcomas) is in direct opposition, being very aggressive, with shortage of plexiform vasculature, important cytological atypia and abundant mitotic figures [4]. Usually, extraterine extension is already present when high-grade ESS is diagnosed, and survival is up to two years (three years after hysterectomy). Because of this, histopathology diagnosis is very important for prognosis. Still, there is no current proof that the mitotic index of 10 or more per 10 high-power fields is a bad prognostic finding in a neoplasm that is otherwise a typical low-grade ESS. A small percentage of occurrences have characteristics from both low-grade and undifferentiated endometrial stroma sarcoma and because of that their classification is disputed [4, 5]. Low-grade ESS can look as a solitary, well outlined and mostly intramural mass, but extensive penetration of the myometrium is more common, with development to the serosa in approximately 50% of the cases [12]. The sectioned surface looks yellow to tan, and it has a softer consistency than the usual leiomyoma. Sometimes cystic, myxoid degeneration, necrosis and hemorrhage are encountered. Extraterine extension is discovered in 1/3 of patients at the time of hysterectomy [13]. The histopathology appearance of the low-grade ESS is frequently a densely cellular tumor made of uniform, oval to spindle-shaped cells [12, 13]. By definition, significant atypia and pleomorphism are absent. The proliferating cells are perfused from an abundant network of small arterioles similar with spiral arterioles [3, 13]. Cells with foamy cytoplasm and endometrial type glands occur in some cases of endometrial stromal tumors. Sex cord-like stromal cells, myxoid and fibrous degeneration may appear [4, 5]. Perivascular hyalinization with a stellate pattern and a dense network of reticulin fibrils occur in some cases [5, 12]. Necrosis is typically not seen or in conspicuous. Regions where there is hard to differentiate between stromal and smooth muscle can become endometrial stromal tumor. If 30% or more of the tumor includes smooth muscle component then it is a mixed endometrial stromal and smooth tumor [6]. On a curettage specimen, it is usually impossible to distinguish low-grade endometrial stroma sarcoma from a stromal nodule or a highly cellular leiomyoma [2, 3]. The stromal nodule is a solitary, well delineated, round or oval, fleshy nodule with a yellow to tan sectioned surface. The stromal nodule can be intramural without any connection to the endometrium, polypoid and other lesions involve both the endometrium and myometrium [13]. The histological aspect is similar to low-grade ESS, the only difference being the absence of infiltrative margins. Rare fingerlike projections that do not pass 3 mm are acceptable. The differential diagnosis is made with low-grade ESS and highly cellular leiomyoma [7]. For this are used additional IHC tests. The presence of focal neoplastic smooth muscle bundles and large, thick walled vessels help us to differentiate an atypical leiomyoma from a stromal nodule. Also, we have a strong immunoreactivity with desmin and h-caldesmon and a low reactivity with CD10 [14]. Both the stromal nodule and low-grade ESS neoplastic cells have positive immunoreactivity for vimentin, CD10 and at least focally for actin. Usually, they are negative for desmin and h-caldesmon, but not each time [14]. Low-grade ESS is most of the times positive for both ER and PR. Rarely, low-grade endometrial stromal tumors, especially the ones
Endometrial stromal sarcoma in a 27-year-old woman. Case report and literature review

with a sex-cord pattern cells, may be immunopositive for α-inhibin, CD99 and cytokeratin [15]. Undifferentiated endometrial sarcomas are characterized by important cellular atypia and abundant mitotic activity, frequently including atypical forms. Different from typical growth pattern and vascularity from a low-grade ESS, in high-grade ESS there are an infiltrative pattern and replace of the myometrium [7, 16]. They look like the sarcomatous component of a carcinosarcomas, and because of this, carcinosarcoma and other specific sarcomas should be ruled out with adequate sampling. These sarcomas usually have aneuploidy with an S-phase fraction greater than 10% and are negative for ER and PR [16]. Treatment is determined by the histopathological pattern and by the staging of disease. Recommended management of ESS is generally surgical, both to establish the final histopathological diagnosis as well for treatment. Hysterectomy with bilateral salpingo-oophorectomy but without lymphadenectomy represents standard treatment for early stage of ESS [16]. Lymphatic or adnexal infiltration is present in about 3% of early stage in ESS [17, 18]. In a case series of a 1396 patients, adnexectomy and lymphadenectomy failed to be independent prognostic factors for survival [19]. In a premenopausal women, considering the adverse effects of early surgical menopause, a simple interanexial hysterectomy it may be a variant of treatment in a low-grade ESS [17]. However, in all other stages, total hysterectomy with bilateral salpingo-oophorectomy is recommended. There is a high rate of lymphatic spread reported in high-grade ESS [19], therefore, some gynecologists recommend routine lymphadenectomy in advanced stages. In our case, after reviewing the literature, we found only very few cases of ESS in young women less than 30 years old and because some authors support the idea that there is a high risk of dissemination at the level of the adnexa and the recommendation of routine adnexectomy, we performed bilateral salpingo-ovarectomy with bilateral pelvic lymphadenectomy extended lumbaoortic and interaortico-cava. Lymph node dissection provides information about prognostic and treatment management. Adjuvant treatment consists of radiotherapy and hormone therapy. Brachytherapy with or without pelvic radiation can be used in FIGO stage III and stage IV disease or in recurrent cases [20, 21]. Almost all ESS show ER and PR, so postoperative hormone therapy with Medroxyprogesterone is a therapeutic standard in these cases. Meta-analysis from large clinical trials is still necessary for determine prognosis and proper treatment strategy of ESS.

Conclusions

ESS is a very rare uterine tumor that usually appears at the woman in peri- or postmenopause. The confusion is generally with uterine leiomyoma. Final diagnosis in established only by histopathology exam of uterus and sometimes by extended immunohistochemical tests. The prognosis of these tumors is variable after surgery, with ESS benefiting of a better prognosis compared to leiomyosarcoma or undifferentiated endometrial sarcoma. A rapid diagnosis and timely surgical intervention must be a therapeutic standard in these cases. Due to various presentations and the rarity of this gynecological pathology, it is difficult to complete randomized clinical trials to determine the optimal management of the treatment. It is essential that these tumors, who have a propensity for late recurrence, to be monitored over the long term.

References


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