ENDOMETRIAL STROMAL SARCOMA – RARE UTERINE TUMOR
A case report and literature review

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Summary. Endometrial stromal sarcoma (ESS) is uncommon uterine malignant tumor and makes approximately 0.2% of all gynecological malignancies. It is the rarest tumor in the group of mesenchymal uterine tumors. Diagnosis may be difficult, since differentiation between several soft-tissue uterine neoplasms such as highly cellular leiomyoma, cellular endometrial polyp, low-grade Mullerian carcinosarcoma and adenomyosis is tricky. Treatment is surgical, hysterectomy and bilateral adnexectomy is obligatory, the role of lymphadenectomy is still controversial. Since ESS is hormone dependent tumor, hormone therapy as adjuvant therapy can be taken into consideration. In this article we present a 57-year-old patient, clinically asymptomatic, with peculiar TV ultrasound feature, and ESS diagnosed on patho-histologically after operation due to presumed benign diagnosis.

Introduction
Group of mesenchymal uterine tumors includes different types of sarcomas (leiomyosarcoma, endometrial stromal sarcoma) and Mullerian mixed malignant tumors (carcinosarcoma). They are histologically and biologically different. Given the rarity of these tumors, they represent “terra incognita” in corpus uteri malignancies. Their many unclear features, and highly aggressive behavior challenge pathologists and frustrate physicians.

Epidemiology
Sarcomas represent 4–9% of all uterine invasive tumors with annual incidence of 1.6–3.3 cases in 100 000 women/year (1,2). Most common histological variety is made up of malignant Mullerian mixed tumors (50%), followed by leiomyosarcomas (30%), and by endometrial stromal sarcomas (10–15%) with incidence respectively 0.82 (malignant Mullerian mixed tumors) 0.64 (leiomyosarcomas) and 0.19 (endometrial stromal sarcomas) per 100000 women/year. Mean age of patients at the time of detection varies depending on histological type. Incidence of leiomyosarcomas increases with the age, with a peak of incidence around the age of 52 years (mean age 48–55) and then incidence declines in older age. Mean age of onset of carcinosarcoma is 62–67 years. Endometrial stromal sarcoma (ESS) intends to appear in younger age compared with other sarcomas and in more than 50% of patients appears before menopause (mean age 41–63) (1–3). In this article we deal with this malignant tumor.

Pathogenesis, biology and cytogenetics
The pathogenesis of ESS is unknown, but as ESS are hormone sensitive tumors, a state of high estrogen could act as a growth stimulus. Exposure to tamoxifen, unopposed estrogens, and conditions such as polycystic disease of ovary is implicated in occurrence of this tumor. Increased incidence of ESS is noticed in women of black race (4). The origin and biology of stromal sarcomas are poorly understood. There is a relation between chromosomal aberrations and endometrial sarcomas. Specific translocation t (7;17) (p15; q21) was described in most of the ESS (12). Chromosomal deletion on 7p was the most common finding (55.6%) in ESS and may play a role in tumor development and progression (13). These tumors are diploid with a low S-phase fraction (11). An important key to improve the knowledge of tumorigenesis of ESS is identification and characterization of genes that are mutated in this rare tumor and that are responsible for altered cell cycle. Recently, some new, sophisticated techniques such as cDNA arrays together with PCR (Polymerase chain reaction is a technique to make many copies of a specific DNA region in vitro) and immunohistochemistry enabled us to identify more than 300 genes mutated in stromal endometrial sarcoma. Among most significantly downregulated genes where those of SFRP proteins, protein 4 (Secreted frizzled–related protein4/ SFRP4). SFRP4 is a member of the SFRP family that contains a cysteine-rich domain homologous to the putative (supposed, assumed) Wnt-binding site of Frizzled proteins. SFRP act as soluble modulators of Wnt-signalling (Wnt – acronym in the field of genetics that stands for “Wingless/Integrated”). The Wnt-signalling pathways are a group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors. Wnt-signalling is a complex cascade of heterogeneous molecules that play an important role in development of different organs (i.e. organogenesis). And more,
there is evidence that mutations of Wnt–signaling is responsible for tumorigenesis in different organs. There is a proof that SFRP4 plays a role in the sequence of Wnt-signalling through beta-catenin, one multifunctional protein that is fundamental for tumor suppressing. Recently it has been demonstrated that expression of beta-catenin is adjusted in opposite way to SFRP4 and is increased both in ESS and UES. According to this newly discovered fact it has been suggested that SFRP4 could be a possible onco-suppressor involved in deregulation (mis regulation) of Wnt sequence and in pathogenesis of ESS and UES (12,13,15).

Pathohistology

ESS where, for a long time, subdivided in high grade and low grade, in relation to number of mitosis (6,9). Subsequently the traditional classification of ESS has been replaced, and high-grade tumors without recognizable evidence of a definite endometrial stromal phenotype are now termed undifferentiated endometrial sarcomas (UES) instead of high-grade ESS. In the latest 2003. WHO classification, endometrial stromal tumors are divided into:

a) Endometrial stromal nodule (ESN)
– well circumscribed, soft, non-encapsulated neoplasm – tan to yellow cut surface – M/E non-infiltrating border – lobulated or finger like projections into the myometrium that are less than 3 mm long and less than 3 in number

b) Low-grade endometrial stromal sarcoma (LGESS or ESS)
– irregular nodular growth involving the endometrium with varying degrees of permeation to myometrium including warm like plugs of tumor that fill the myometrial veins (often extending to parametria veins) – proliferation of uniformly small cells closely resembling those of endometrial stroma in the proliferative stage. The cells have scanty cytoplasm, oval to round nuclei and unnoticeable (unremarkable) nucleoli – significant atypia and pleomorphism are absent – mitotic activity is usually less than 5/10 high power fields

c) Undifferentiated endometrial or uterine sarcoma (UES)
– polypoid, fleshy, grey to yellow endometrial masses and often show prominent hemorrhage and necrosis – marked cellular atypia and abundant mitotic activity, often including atypical forms – they lack the typical growth pattern and vascularity of low-grade ESS and displace the myometrium in contrast to the infiltrative pattern of low-grade ESS – they resemble the sarcomatous component of carcinosarcoma

In this classification the differentiation between low-grade and undifferentiated tumors is not made on mitotic count but based on nuclear pleomorphism and necrosis (11,15,66). Since myometrial and vascular invasion are the two features that help us to differentiate ESS from ESN and the UES resembles the sarcomatous component of carcinosarcoma (UES represents a high-grade sarcoma that lacks specific differentiation and bears no histological resemblance to endometrial stroma), extensive sampling of the tissues is required for confirmation of diagnosis (5,6). Macroscopically ESS is presented like a single, well defined intramural mass with or without polypoid component, or more frequent like one marked adenomyosis which invades myometrium and extends at serosa in approximately half of cases. Surface is yellow-brownish, on cut grayish. Lesion has fluffy consistence unlike a classic leiomyoma, and doesn’t present protuberant, bulgy aspect characteristic for myoma. Rarely there are myxoid or cystic aspects or focal hemorrhages and necrosis (Fig 1).

Diagnosis

Differentiation between several soft-tissue neoplasms demonstrating arborizing vasculature (vascularization) such as highly cellular leiomyoma, cellular endometrial polyp, low-grade Mullerian adenosarcoma and adenomyosis the diagnosis of ESS may become more difficult.

Clinical presentation

The most common symptom of ESS is abnormal uterine bleeding and occurs in about 90% of women. Uterine enlargement shows up to 70 % of cases. ESS sometimes present with pelvic pain and dysmenorrhea. An asymptomatic ESS occurs in 25% individuals. About 30 to 50% of the ESS has extra uterine spread at the time of the diagnosis (16,17).

Immunohistochemistry

CD10 is a cell-surface neutral endopeptidase, seen originally on immature lymphoid cells. Recently, CD10 expression has been shown in several nonhematopoietic neoplasm, including endometrial stromal sarcomas

Hormone therapy

Hormone therapy is expected to be effective in ESS because of estrogen and progesterone receptors in it. Hormones include megestrol/ medroxyprogesterone, gonadotropin releasing hormone (GnRH) analogues, and aromatase inhibitors (40). The mechanism of action of progestins is to bind progesterone receptors and to slow down regulate gene transcription leading to decreased endometrial gland and stromal proliferation. GnRH agonists slows down regulate GnRH receptors in the anterior pituitary gland, leading to a hypoestrogenic state. Estrogen deprivation is most specifically achieved using inhibitors that block the last stage in the biosynthetic sequence, that is, the conversion of androgens to estrogens by the aromatase enzyme. The new generation aromatase inhibitors such as letrozole, when given orally, inhibits peripheral aromatase and causes a marked reduction in circulating estrogens. ESS shows expression of aromatase enzyme and aromatase inhibitors such as letrozole and anastrozole can be used as adjuvant treatment (33,51,52,54).

The literature data related to adjuvant hormone therapy for EES are rare and are based on small number of patients. Particularly there are no studies of stage III, to support use of hormones in therapy. Schwartz et al. suggested use of progesterone (for example megestrol acetate, in dosage 160 mg /day) at least for 24 months in patients with complete resection of tumor (33).

Prognosis

Clinical factors such as age, race, parity, menopausal status and pathological factors including tumor size, tumor stage, nuclear atypia, mitotic activity, tumor necrosis, lymph vascular space invasion, DNA ploidy proliferative activity, and expression of hormone receptors, are to be taken into consideration for prognosis. Prognostic factors for poor survival are: high age (older patients) – age more than 50 years, black race, advanced stage, lack of primary surgery, nodal metastasis, high mitotic count – more than 5 per 10 high-power fields, CD10 negative or low expression and lack of estrogen and progesterone receptors (25,26). Tumor classification is essential for prognosis (16,17,19). If properly classified (since ESS represents a separate clinical entity and has a way much better life expectancy than other sarcomas), the most important prognostic factor is the stage of the disease at the time of detection.
Stage I (Tumor limited to the uterus): IA Less than or equal to 5 cm; IB More than 5 cm
Stage II (Tumor extends beyond the uterus, within the pelvis): IIA Adnexal involvement; IIB Involvement of other pelvic tissues
Stage III (Tumor invades abdominal tissues, not just protruding into the abdomen): IIIA One site; IIIB More than one site; IIIIC Metastases to pelvic and/or paraortic lymph nodes
Stage IV: IVA Tumor invades bladder and/or rectum; IVB Distant metastases

At FIGO stage I, the 5-year survival rate for ESS is 54% to nearly 100%. At stage-II it is 30%. For advanced disease (stage III and IV) the survival is only 11%. As these tumors are indolent (lazy) and have a tendency for late recurrence, long-term follow up is essential. It shall be once in 3 months for the first year after primary treatment. Than half-yearly for next 4 years. Thereafter annual follow up is sufficient (25–27,60).

Recurrent disease

Recurrences develop in one-third to one-half of patients with ESS and are usually limited to the pelvis and lower genital tract. Distant metastasis to lungs and superior abdominal cavity may occur after several years, even more than 20 years. Metastases in brain are rare (54,55). A growth stimulus by estrogens on residual tumor cells may contribute to recurrence. After oophorectomy, estrogens produced by peripheral tissues or exogenous administration in the form of hormone replacement therapy may be a reason for recurrences (56).

There is no standard therapy for patients with recurrent disease. Recurrent ESS has been treated with hormone therapy, radiation, surgical re-excision, or a combination of these modalities (56,57).

Case Report

A 57 years old woman appeared in our Department, send by her gynecologist in primary health care, for peculiar (problematic) ultrasound formation inside myometrium. She had no symptoms, nor major gynecological (problematic) ultrasound formation inside myometrium, by her gynecologist in primary health care, for possible hormone replacement therapy. When it came, I never knew when it will stop... Patient said: “I never knew when menstruation will come, and when it came, I never knew when it will stop...” Her menstrual cycles were irregular all her life. She delivered two healthy children. When transvaginal sonography was performed in our department, within an enlarged uterus (9.1 x 6.9 x 5.3 cm) an unusual, well limited anechogenic formation (structure) 3.5x3 cm showed up inside myometrium, along with two minor (1.5 and 1.7 cm) fibromas; endometrium thickness was 4.5 mm, cavum uteri empty (Figure). Both ovaries normal.

Figure 2. CT of pelvis showed intensive postcontrast display of myometrium with a zone of lower density 3.5 cm which implicates complicated cyst, decomposition of tissue...” (Figure). Blood biochemistry finding, and tumor markers were normal. As a matter of fact, we have never seen such clinical (asymptomatic enlarged uterus) combined with unusual ultrasonic and CT display, (anechogenic, lower density formation within myometrium), so we concluded that it is most likely a colliquifed / liquefied myoma / fibroma. Therefore, according to enlarged uterus, age and parity of patient, total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed.

Pathohistological finding showed endometrial stromal sarcoma. Pathohistological finding: Uterus is enlarged 10x8x4 cm. In uterine cavity protrudes a tumor 4 cm in longer diameter, surface of cut is grayish, (Figure), consistence of tumor is medium solid, in some places soft. Tubal tissue did not show any pathohistological change. In both ovaries some inclusive cysts are visible. Exocervical epithelium is regular. In endocervical area some duplicated subcylindrical reserve cells are visible. Endometrial stroma is sturdy with mostly small tubular glands, coated with cylindric epithelium. Tumor that protrudes into cavity is made of uniformed, oval, atypical cells endometrial stroma type, with expressed vascularization with small regularly (normally) blood vessels. In 1/10 high power fields 1 mitosis is found. In 1/10 high power fields 1 mitosis is found. Immunohistochemistry of tumor cells demonstrate partially positive reaction on CD10, SMA and desmin. Tumor cells in “hot spot” also demonstrate nuclear positivity on estrogen and progesterone receptors in 90% cells. Tumor is partly polyloid, partly in lobulated form, partly in finger like projections invades over than ½ of myometrium. Clusters of tumor cells are within vascular spaces (blood vessels) of myometrium. Conclusion: histological and immunohistochemical analysis correspond to ESS-low grade. Tumor is limited to the wall of corpus uteri (infiltrates ½ of myometrium) and vascular infiltration is present.
Since it was a tumor in stage IA, no further therapy was necessary. Patient is ordered for first follow-up control in 3 months.

Conclusion

Endometrial stromal sarcomas are very rare malignant tumors that make about 0.2% of all uterine malignancies.

A proper preoperative diagnosis is difficult and in most cases the diagnosis is confirmed after hysterectomy for a presumed benign disease.

Therapy is surgical, and includes hysterectomy and salpingo-oophorectomy, with or without lymphadenectomy depending on stage of tumor. Lymph node dissection provides prognostic information and treatment guidance; however, the potential therapeutic value of lymph node dissection remains to be determined.

Patients with sarcoma stromal endometrial with extra-uterine spread of disease, should be submitted to debulking surgery with removal of greatest part of tumor possible and subsequently treated with hormone adjuvant therapy (megestrol acetate 160 mg/day) possibly based on knowledge of hormone receptors status, and up to regression of disease or toxicity of drug itself.

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SARCOMA STROMALE ENDOMETRIALE
– RIJEDAK GINEKOLOŠKI TUMOR
Prikaz slučaja i pregled literature

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Prikaz bolesnice

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