Chapter 3

Uterine Sarcomas: An Updated Overview. Part 2: Endometrial Stromal Tumors

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Abstract

Uterine sarcomas (USs) account for 3–9% of uterine malignant neoplasia and about 5% of all gynaecologic malignancies. Despite their low prevalence, these tumors stimulate a great interest because of their aggressiveness, poor prognosis and high mortality rate. According to the last world health organization (WHO) classification and the International Federation of gynecology and obstetrics committee (FIGO) staging, USs are categorized as pure mesenchymal tumors (endometrial stromal sarcoma, leiomyosarcoma and undifferentiated uterine) and mixed tumors (carcinosarcoma and adenosarcoma). Due to their non-specific signs and symptoms, USs are commonly diagnosed in advanced stage, more often after surgery for a suspected leiomyoma. Although surgery followed by adjuvant therapies represent the common choices for USs, they show poor efficacy due to the early occurrence of metastasis, and the high resistance of tumors to radio-and chemotherapy. Presently, specific expression profiles and new cytotoxic agents are under investigation. In these reviews, we summarized clinical and pathological features, imaging characteristics, therapeutic approaches, genomic and molecular aberration associated with smooth muscle neoplasia (Part 1) and endometrial stromal neoplasia (Part 2); the goal is to understand the biology and the molecular signature of these tumors, in order to focus on their best management.

Keywords: uterine sarcomas, mesenchymal tumors, uterine malignant neoplasia, uterine stromal sarcomas

1. Introduction

Endometrial stromal sarcomas (ESSs) are mesenchymal malignancies mainly occurring in uterine corpus. Alternative origins, such as ovary and peritoneum, have been described. Pathogenesis of ESSs has been widely debated. The rarity of this neoplasia contributed to the difficulty in classifying them into clinically meaningful categories. All started in 1966 with Norris and Taylor, who classified ESS into low-grade and high-grade neoplasia, basing on the degree of mitotic activity [1]. Following studies demonstrated the irrelevant value of mitotic activity as prognostic factor. In 1982, Evans understood the importance of separating tumors with endometrial stromal differentiation from poorly differentiated endometrial sarcoma [2]. Studies from Chang et al. demonstrated that a combined assessment of cytological/nuclear atypia and mitotic index could better provide prognostic information than either feature alone [3].

In 2003, WHO abolished "high-grade" category and adopted a classification based on two categories: low-grade ESS (histological resembling proliferative endometrial stroma) and undifferentiated endometrial sarcoma (UES) [4]. The main perplexity with 2003 WHO classification was related to the heterogeneity of undifferentiated endometrial sarcomas category, which enclosed tumors with different morphology, clinical behavior and outcome. In the following years, cytogenetic and molecular investigations helped to redefine ESSs and, in

FIGO stage	Definition
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extended to the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or paraaortic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invades bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

FIGO, International Federation of Gynecology and Obstetrics Committee.

Table 1. 2009-revised FIGO staging system for endomerial stromal sarcomas.

2014, WHO identified four groups of endometrial stromal neoplasia: endometrial stromal nodule-ESN, low-grade endometrial stromal sarcoma-LGESS, high-grade endometrial stromal sarcoma-HGESS, and undifferentiated uterine sarcoma-UUS [5]. Each one demonstrated peculiar molecular signatures, morphological characteristics, and prognosis. FIGO staging system ESSs was revised in 2009 (**Table 1**) [6].

Endometrial stromal sarcoma accounts for approximately 10% of all uterine sarcomas and about 0.2% of all uterine malignant neoplasia. At presentation, the vast majority of patients are in the fifth decade; among these, about 50% are premenopausal women [7]. Although molecular mechanisms involved in the genesis of ESSs are not clear yet, obesity, diabetes, early menarche, and tamoxifen intake have been associated with an increased risk of developing this neoplasia [8]. Abnormal uterine bleeding and pelvic/abdominal pain represent the main symptoms of ESSs, which may be present as uterine mass or endometrial polyp. In the latter cases, endometrial biopsy is more likely to be diagnostic [8]. ESS may most often be an incidental finding in patients undergoing hysterectomy for other reasons; in such cases, pulmonary metastases may be detected at the time of the diagnosis [8].

2. Endometrial stromal nodule (ESN)

ESNs are defined as benign stromal tumors of the uterus. They occur in women ranging from 31 to 86 years, with a mean of about 50 years [9].

2.1. Macroscopic features

ESNs are more common in uterine corpus than in the cervix. They show well defined but expansible margins, absent/minimal myometrial invasion, and no lymph vascular invasion. If myometrial or lymph vascular invasions are present, tumor should be diagnosed as LGESS. ESN may occur as an intramural mass centered in the myometrium, or as a polypoid tumor protruding into the endometrial cavity [8]. On gross examination, ESN size ranges from 1 to 22 cm. The nodule is well demarcated, even if finger-like projections (<3 in number and <3 mm in maximum extension) into adjacent myometrium may occur. In these cases, some pathologists diagnose this neoplasia as "endometrial stromal nodule with limited myometrial infiltration" [8]. The tumor shows a uniform tan-to-yellow soft cut surface; cysts formation, infarct-type necrosis, and hemorrhage are uncommon. If present, cysts may be secondary to necrosis and hemorrhage. Rarely, ESN may exclusively be cystic [8].

2.2. Microscopic features

ESN is composed of cells with uniform round-ovoid nuclei, small nucleoli, and scant-moderate eosinophilic cytoplasms. This diffuse proliferation of monotonous "blue cells" resembles proliferative phase of endometrial stroma (**Figure 1A** and **B**). Cytological atypia is minimal, and although mitotic rate is usually low (up to 5 mitosis/10 HPF), a higher count does not exclude ESN diagnosis [8]. A rich and arborizing network of small arterioles

around which neoplastic cells are concentrically arranged also characterizes ESS [8]. Thick-walled vessels may be present in a minority of cases. The presence of collagen bands or plaques uniformly dispersed in the context of the tumor is often seen (**Figure 1A**). Foamy histiocytes, singly or in clusters are also described, as well as cholesterol clefts. ESNs present some variants including smooth muscle, skeletal muscle, and sex-cord stromal differentiations [8].

2.3. Immunohistochemistry

Vimentin, CD10, actins, WT1, ER, and PR are typically positive in ESN. Rarely, the neoplasia may be CD10 negative. Although, smooth muscle tumors and ESN demonstrate an overlapped immunophenotype, CD10, desmin, h-caldesmon, smooth muscle heavy chain myosin, and HDAC8 facilitate the differential diagnosis. In particular, areas of smooth muscle differentiation stain positive for desmin and h-caldesmon, although areas of stromal differentiation may be desmin positive also; such areas show a typical perinuclear cytoplasmic pattern [8].

2.4. Differential diagnosis

ESN with smooth muscle differentiation can be misdiagnosed as endometrial stromal sarcoma invading the myometrium, due to the presence of interdigitating smooth muscle cells misinterpreted as myometrial invasion [9]. Differential diagnosis would also be needed between ESN, highly cellular leiomyoma, LMS, and LGESS. Highly cellular leiomyoma characteristically shows focal fascicular pattern, margins with a cleft-like zone, and contains thick-walled blood vessels [8]. Uterine LMS does not present as a low-grade neoplasia [8]. Finally, since morphology demonstrates to be not useful in distinguishing between ESN and LGESS, diagnosis relies on the exclusion of myometrial and lymph vascular invasion [8]. A definitive diagnosis of ESN should be provided after a careful examination of tumor borders; thus, specimens from hysterectomy are needed.

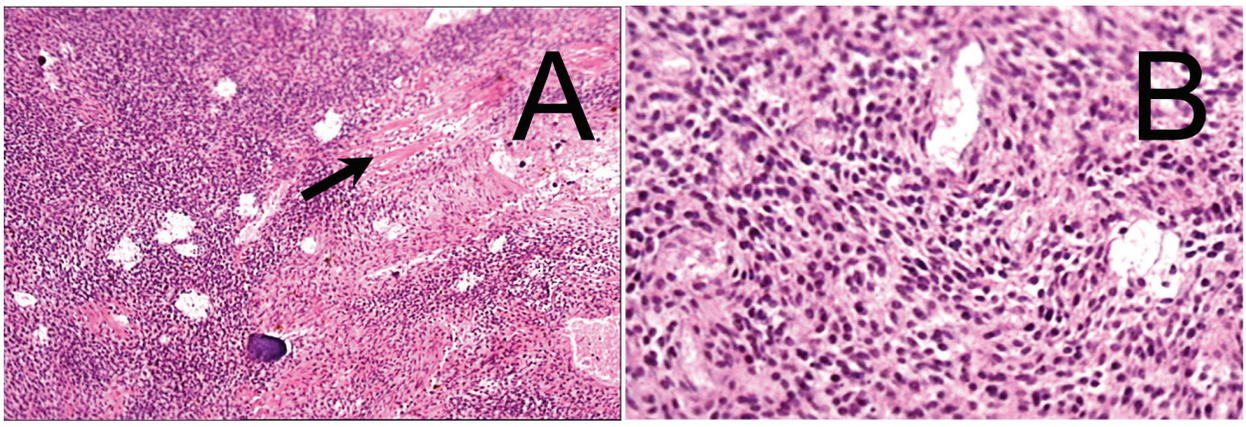

Figure 1. Endometrial stromal nodule. (A) Diffuse proliferation of monotonous blue cells resembling proliferative phase of endometrial stroma. Collagen bands dispersed in the context of the tumor (arrow), EE, 10×. (B) Neoplastic cells show uniform round-ovoid nuclei and scant-moderate eosinophilic cytoplasms, EE, 20×.

On curettage specimens, the distinction between ESN and LGESS is quite impossible. Finally, in ESNs with "limited infiltration," the infiltration is not widespread as showed by LGESS [8].

2.5. Molecular features

ESN is characterized by the chromosomal translocation *t(7,17) (p15;q21)*, resulting in the formation of JAZF1-SUZ12 fusion gene. JAZF1-SUZ12 gene has been found in about 50% of ESNs and in LGESS [10].

2.6. Keypoints

- ESN may demonstrate focal finger-like projections toward myometrium. To confirm ESN diagnosis, the projections should be <3 in number and <3 mm in their maximum extension.
- Both ESN and LGESS share the same genetic aberration; thus, the presence of *t(7;17)* cannot be used to distinguish between the two neoplasia.
- Correlation between immunostain results and morphology may help in distinguishing between ESN with smooth muscle differentiation and pure smooth muscle tumor.

3. Low-grade endometrial stromal sarcoma (LGESS)

This neoplasia is composed of cells resembling those of endometrial stroma during proliferative phase, associated with a broad network of arteriolar-like vessels. The tumor shows infiltrative "tongue-like" growth into the myometrium, with or without lymph vascular invasion.

Accounting for about 0.2–1% of all uterine malignancies, LGESS represents the second most common uterine sarcoma. It is more common than ESN. The age range is similar to that of ESN, more often occurring in perimenopause. The median age is 52 years. No race is favorite [10]. Being a slow-growing tumor with an indolent clinical course, LGESS shown no-specific signs; they include vaginal bleeding and pelvic pain. LGESS most frequently occurs in the uterine corpus, even if extra uterine locations such as ovary pelvis, abdominal cavity, vulva, and vagina are possible. Association with endometriosis has been described [11].

3.1. Macroscopic features

The vast majority of LGESS are diagnosed on hysterectomy that has to be considered as a diagnostic and therapeutic approach. Curettage or myomectomy specimens are not useful, since LGESS diagnosis should substantially rely on the evaluation of the tumor/myometrial interface [8]. Fertility-sparing approaches should be used only in carefully selected cases. Grossly, LGESS is typically poorly defined, but well-circumscribed borders might be found

when myometrial invasion is limited. Neoplastic mass may present as intracavitary or intramyometrial. Similarly to ESN, the cut surface is fleshy with tan-to-yellow or white color. Firmly consistency is reported in the presence of extensive fibrous stroma. Cystic formation, as well as areas of hemorrhage and necrosis might be present [8]. Rarely, LGESS appears as a pure cystic mass.

3.2. Microscopic features

LGESS is characterized by the irregular interface with the myometrium (**Figure 2A**). Myometrial invasion and lymph vascular "tongue-like" patterns represent the cardinal features to put differential diagnosis between LGESS and ESN [8]. Cytological features are identical to those of ESN: monotonous "blue cells," with scant cytoplasm, uniform oval-spindle nuclei, and small nucleoli, typically growing in sheets or storiform patterns (**Figure 2B**). Vessels are thin with hemangiopericytoma-like morphology or, less commonly, thick and placed at the periphery of the neoplasia. Nuclear atypia is not significant and mitotic count is usually less than 5 mitosis/10 HPF ([8], p. 1). Like in ESN, alyne bands, cholesterol clefts in the context of areas of necrosis, and cystic formation may be encountered. Several histological variants of LGESS have been described. In smooth muscle type, smooth muscle component accounts for more than 30% of all uterine mass [8]. On gross examination, this component appears as a firmly area. Microscopically, smooth muscle differentiation is characterized by pink irregular islands of slightly epithelioid cells. Starburst pattern, with a central area of hyalinization and collagen bands radiate toward the periphery, may also be seen [8]. In myxoid and fibroblastic type, neoplastic background is typically hypocellular. Fibroblastic component has been reported in about 50% of ESS with *t(10,17)*. In such cases, a more aggressive behavior has

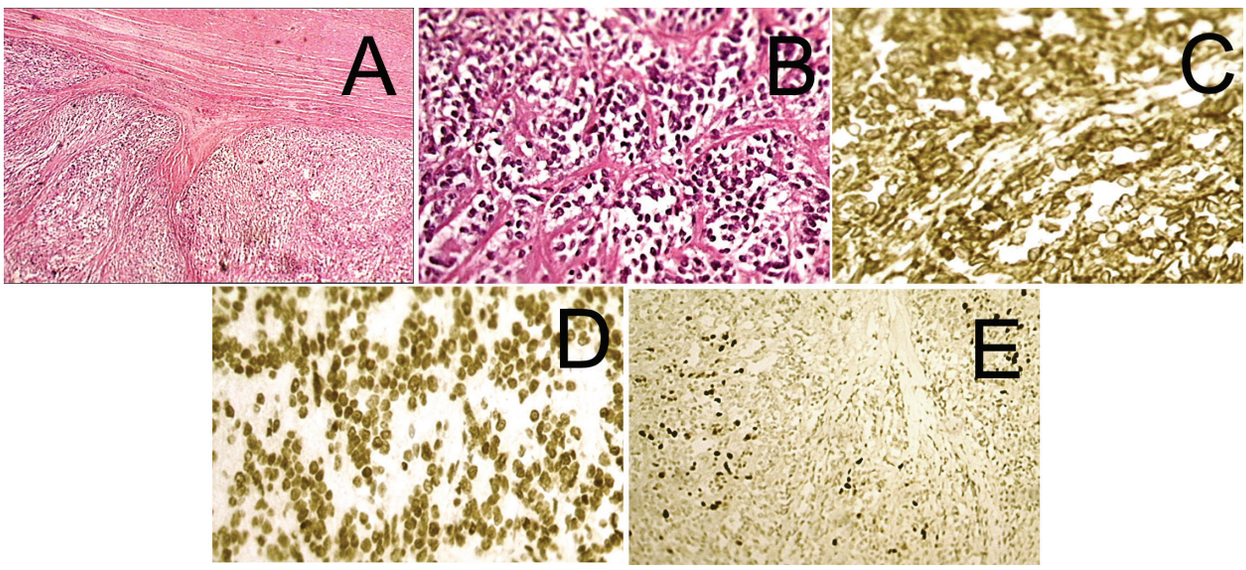

Figure 2. Low-grade endometrial stromal sarcoma. (A) Irregular interface with the myometrium, with 'tongue-like' patterns of invasion, EE, 4×. (B) Monotonous blue cells, with scant cytoplasms and uniform oval-spindle nuclei, EE, 20×. (C) CD10 positive stain, 20×. (D) Estrogens receptor stain, 20×. (E) MIB1 index, 10×.

been demonstrated [8]. Sex cord-like elements, consisting in anastomosing cords, trabeculae, islands, nests, tubules or sheets of cells resembling the pattern typically seen in granulosa and Sertoli ovarian cell tumors, may also be encountered in LGESS. Sex cord-like cells are usually present within the endometrial stroma. Not infrequently, the areas of smooth muscle differentiation may also co-exist [12]. **Glandular elements** showing endometrioid morphology have also been reported in LGESS. Cells have cuboid-columnar shape; with eosinophilic or rarely clear cytoplasm and minimal cytological atypia [1]. **Epithelioid variant** is characterized by cells with oval-polygonal appearance and abundant, often granular, cytoplasm [8]. **Rhabdoid type** shows cells with large and eosinophilic cytoplasmic inclusions, eccentric vesicular nuclei, and prominent nucleoli [13].

Antibody markers	LGESS	HGESS	UUS	UTROSCT
Smooth muscle actin			+, patchy	+
Desmin	+		+, patchy	+
h-cardesmon	+			+
EMA	±		+, patchy	
CD10	++	—	±	
CD34	—			
CD44				
Cytokeratins	±		+, patchy	+
HDAC8				
ER	+	—	- or weakly +	
PR	+	—	- or weakly +	
p53			+	
p21				
Bcl-2				
MIB1			high percentage	
p16			+	
Inhibin				+
S100				
c-kit		+		
Cyclin D1	—	±	—	

LGESS, low-grade endometrial stromal sarcoma; HGESS, high-grade endometrial stromal sarcoma; UUS, undifferentiated uterine sarcoma; and UTROSCT, uterine tumor resembling an ovarian sex-cord tumor.

Table 2. Immunohistochemical features of uterine endometrial stromal tumors.

3.3. Immunohistochemistry

No single marker demonstrated high specificity. Thus, a panel of antibodies should be used (**Table 2**). It is also important to take into account the intensity and the distribution of positive results and to correlate them with histological features and gross findings. CD10 is a very helpful marker, since its expression is generally strong and diffuse in typical LGESS (**Figure 2C**). Positive stain for WT1, ER, and PR is observed in more than 80% of LGESS (**Figure 2D**) [8]. Ki67 mitotic index is high (**Figure 2E**). Cyclin D1 is negative or focally positive [14]. However, in *t(10;17)*, LGESS CD10 may be negative or weakly and focally positive [14–27]. *t(10,17)* LGESSs are frequently negative for ER and PR too [15]. Expression of nuclear β-catenin has been reported in about 40% of *t(10;17)* LGESS, often in association with cyclin D1 positivity [15]. In general, LGESS variants show immunohistochemical pattern concordant with the type of cellular differentiation [15]. Epithelioid LGESS is typically positive for desmin and h-caldesmon, often positive for keratin and EMA, and negative for cyclin D1 [8]. Expression of smooth muscle actin, desmin, and h-caldesmon may be present in typical LGESS [8]. Since CD34 is almost never expressed in uterine LGESS, this marker is helpful to diagnose LGESS of extra uterine sites [15]. p53 is typically absent in LGESS, while it has been reported in HGESS and USS ([8], p. 1). Finally, expressions of PDGFR-α and PDGFR-β were, respectively, found in 50 and 42% of LGESSs [16].

3.4. Differential diagnosis

Differential diagnosis between ESN and LGESS has been previously described. A common problem is to differentiate LGESS from highly cellular leiomyoma. Careful macroscopic and microscopic assessment is needed to put the right diagnosis. Leiomyoma usually forms fascicles of spindle cells with elongated cigar-shaped nuclei; blood vessels are small and do not show the typical arteriolar morphology usually seen in LGESS. In addition, using a panel of antibodies including CD10, desmin, and h-caldesmon, differential diagnosis may be facilitated. It would be always important to correlate immunostain results with morphology [8]. Both LGESS and intravenous leiomyomatosis may show vessel invasion; however, microscopic examination helps to differentiate these entities, since the latter is characterized by a fascicular pattern with large and tick blood vessels [8]. Epithelioid smooth muscle tumor can resemble the smooth muscle variant of LGESS. However, the former lacks of the typical vasculature seen in the endometrial stromal neoplasia. ESS with myxoid differentiation may be confused with myxoid LMS, since both show hypocellularity and a similar pattern of myometrial infiltration. However, LMS usually demonstrates cells with high-grade atypia and brisk mitotic activity [8].

Distinction between LGESS with sex cord-like differentiation and Uterine Tumor Resembling an Ovarian Sex-Cord Tumor (UTROSCT) has to be done. UTROSCT is a rare mesenchymal neoplasm composed of epithelial-like cells showing the typical patterns of the ovary sex-cord stromal tumors; its behavior is benign, without risk of recurrences [17]. Differential diagnosis should rely on the presence of areas of conventional stromal

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neoplasia in the LGESSs. Obviously, the distinction cannot be done on biopsy or curettage specimens. Immunohistochemistry may be helpful when using a panel of antibodies including inhibin, calretinin, and Melan A [8]. Stromal component of an adenosarcoma may be morphologically and immunohistochemically identical to that of ESS. However, while the stromal component of adenosarcoma is strictly associated with the epithelial component, in LGESS, glands are few and randomly placed [8]. Finally, GIST comes into differential diagnosis with LGESS; in these cases, a panel of antibodies including c-kit and DOG1 should be used [18].

3.5. Molecular features

The vast majority of LGESSs harbor chromosomal rearrangements.

As previously described, the most common genetic aberration is the *t(7;17) (p15;q21)* translocation that has been found in about 80% of LGESSs and morphological variants. *t(7;17) (p15;q21)* results in JAZF1-SUZ12 gene fusion [19]. Being detected in both ESN and LGESS, *t(7;17)* translocation would represent an early event in the development of ESS. It has been hypothesized that ESS would originate from a benign stromal proliferation, being neoplastic progression the result of additional events [20]. As a counterpart, the lack of JAZF1-SUZ12 gene in most cases of undifferentiated endometrial sarcoma would suggest the existence of a different pathogenesis leading to ESS. Translocation *t(6;17) (p21;p22)* represents the second most common genetic abnormality in LGESS, being the *t(6p;10q,10p)* the third. Other gene fusions, which have been detected in association with ESSs, are JAZF1/PHF1, EPC1/PHF1 MEAF6-PHF1, ZC3H7-BCOR, and MBTD1-CXorf67 ([21], p. 109). JAZF1, SUZ12, PHF1, and EPC1 gene fusions have also been detected in other types of benign and malignant neoplasia [21]. Rearrangement of the X chromosome has also been seen in LGESS, in association with two different transcripts [22]. All of the genes involved in the previously listed chromosomal translocations are implicated in transcriptional regulation. Translocations would lead to oncogenic effects starting from deregulation of transcriptional mechanisms in endometrial stromal stem cells [23]. All of the genetic fusions seem to be equivalent in inducing oncogenic events, since LGESSs having different genotypes show similar clinical behavior. Microscopically, all of the JAZF1 LGESSs demonstrate tongue-like myometrial invasion accompanied by vascular invasion [23]. From a prognostic point of view, both JAZF1-LGESS and LGESS without genetic rearrangements (wild LGESS) usually have a low incidence of recurrences [23]. Finally, although no correlation has been found between morphological variant of LGESS and a specific chromosomal abnormality, PHF1 genetic rearrangement has been frequently observed in LGESS with sex cord differentiation [24].

3.6. Therapeutic approaches

Patients with LGESS are usually treated with hysterectomy plus bilateral salpingo-oophorectomy, the latest to avoid the secondary stimulation of the tumor by ovarian hormones. Younger patients desiring to preserve fertility can be treated with hormonal therapy or aromatase

inhibitors. The adjunct of gonadotropin releasing hormone (GnRH) may reduce ovarian synthesis of estrogens [25]. Since low-grade ESSs show low response rates to conventional CT, there is no evidences supporting its use ex adiuvantibus. On the other hand, the presence of estrogens and progesterone receptors in about 80% of the LGESS would give the opportunity to reduce the recurrence rate and risk of relapse using adjuvant endocrine therapy. Hormone therapy with progestin, aromatase inhibitors, and analogues of the gonadotropin-releasing hormone has become an effective post-surgical treatment in patients with low-grade ESS [26]. Particularly, aromatase inhibitors are becoming the treatment of choice, since progestin is poorly tolerated due to side effects. The duration of hormonal therapy should be protracted for 3–5 years after surgery [26]. Tumors with *t(10;17)* translocation, typically not responding to conventional treatment, should be treated with a more aggressive therapy such as RT and CT combination [23]. Finally, in LGESS showing immunohistochemical positivity for PDGFR-α and PDGFR-β, the PDGF signaling pathway may be considered as a useful therapeutic target for imatinib [26].

3.7. Prognosis

Stage is the most significant prognostic indicator in LGESS. Disease-specific survival is approximately 80–90% at 5 years and 70% at 10 years [26]. Patients with stage I LGESS show a survival rate of about 100% at 5 years and 90% at 10 years; women presenting with high-stage disease have a survival rate of 40%, which is constant at 5 and 10 years [8]. Clearly, tumor grading is also a powerful predictor of disease recurrences, which are observed in about 50% of the patients especially in pelvis, abdomen, and lungs [8]. Recent data demonstrated that stage and mitotic activity correlate with the outcome of the neoplasia, while cytological atypia correlates with increased relapse of LGESSs [8]. A tumor showing both severe cytological atypia and high mitotic rate, with or without the typical endometrial stromal sarcoma growth pattern, should be considered as USS [8]. Cases of USS arising in a background of LGESS have been rarely reported [27]. A tumor with more than 10 mitotic figures/10 HPF without severe cytological atypia should be considered as a pure LGESS. Finally, prognosis of JAZF1-LGESS and wild-LGESS are similar, since no genotype-specific target therapy exists yet [25].

3.8. Keypoints

- Like ESN, LGESS may be well circumscribed on gross examination. Thus, the adequate sampling of the interface neoplastic border/myometrium is imperative to reach a correct diagnosis.
- Biopsy, curettage or myomectomy specimens are not useful.
- Cytological features of LGESS are identical to those of ESN. Nuclear atypia is not significant, mitotic rate is usually less than 5 mitosis/10 HPF, nuclear pleomorphism is absent, and necrosis is rarely present.
- A panel of antibody may help in diagnosis, in tight correlation with gross and microscopical features. In LGESS, cyclin D1 is negative-to-focal, and CD10 and ER/PR are diffusely positive.

- LGESS demonstrate histological variants.
- Since sex cord-like differentiation may occur in LGESS, UTROSCT should be excluded by extensive samples.
- Intravenous leiomyomatosis can be highly cellular and often mimics a LGESS. Intravascular component with cleft-like spaces, fascicular growth pattern, proliferation of spindle cells colonizing the wall of the veins, and thick-walled blood vessels may help to diagnose the former.
- The most common chromosomal translocation in LGESS is *t(7;17) (p15;q21)*, resulting in JAZF1-SUZ12 gene fusion.
- Stage and brisk mitotic activity correlate with the outcome, while cytological atypia correlates with increased relapse.

4. High-grade endometrial stromal sarcoma (HGESS)

The 2014 WHO classification of uterine mesenchymal tumors re-introduced HGESS as a distinct entity [28]. Lee et al. identified a fusion between the tyrosine 3/tryptophan5-monooxygenase gene YWHAE from chromosome 17p13 and the NUT family member gene NUTM (previously known as FAM22) from chromosome 10q22 [29]. The identification of the YWHAENUTM2A/B (also designed as YWHAE-FAM22A/B) gene fusion as a recurrent genetic event in ESS with more aggressive behavior, provided the basis to create a category of ESS intermediate between LGESS and UUS (**Table 3**). Before 2014, HGESS was enclosed in the "undifferentiated endometrial sarcomas" group [30]. Kurihara et al., underlining the heterogeneity of this group, emphasized the importance to distinguish between tumors with nuclear uniformity and YWHAE rearrangement, and tumors with nuclear pleomorphism, more complex karyotypes, and frequent p53 alterations [8]. Separation between LGESSs and HGESSs was also important, due to the peculiar clinical aggressiveness of the latter [31]. The age of women affected by HGESS ranges from thirty to seventy years, with a mean of 50 years. HGESS most commonly presents with abnormal uterine bleeding and symptoms related to extra-uterine spreads [8].

	ESS	**USS**
Age at presentation	Perimenopausal	Postmenopausal
Cytology	Monomorphous	Polymorphic and highly atypical
Growth pattern	Infiltrative	Expansive
Vascular pattern	Intravascular growth	Vascular invasion
Hormonal receptors	Estrogens-related	Not estrogens-related
Prognosis	Good, late recurrence	Poor, early recurrence and distant metastasis

ESS, endometrial stromal sarcoma; USS, undifferentiated uterine sarcoma.

Table 3. Differential diagnosis between endometrial stromal sarcomas and undifferentiated uterine sarcomas.

4.1. Macroscopic features

HGEESs appear as an intracavitary polyp or poorly circumscribed mural plaques-like masses, with a median diameter of 7.5 cm. The cut surface is fleshy and often associated with areas of hemorrhage and necrosis [8]. Being destructive, myometrial invasion of HGESS is different from that of LGESS, which is permeative. Extrauterine extension is frequent [8].

4.2. Microscopic features

At low-power magnification, the morphology of HGESS does not exactly look like the proliferative endometrium. HGESS is characterized by a monomorphic proliferation of round cells arranged in a vaguely nested or pseudo-glandular pattern [8]. The infiltrative growth pattern and the vascularization typical of the LGESSs coexist, together with the features of destructive invasion of the outer half of the myometrium. The tumor often contains both morphologically low- and high-grade areas. Low-grade areas are hypocellular and composed by a uniform population of neoplastic spindle cells, with no apparent nuclear pleomorphism [8]. These areas may also show myxoid appearance. High-grade areas typically show a population of closely packed large (epithelial-like) cells, arranged in nests or cords (**Figure 3A**). The vascular pattern is delicate and arborized (**Figure 3B**) and is different from the spiral arteriolar-like pattern characteristically seen in LGESS. Concentric arterioles may occasionally be present [8]. At high magnification, HGESS cells show eosinophilic cytoplasms; nuclei are large, with irregular contours and prominent nucleoli (**Figure 3A** and **C**). Mitotic activity is brisk. In non-rearranged (wild) HGESS, mitotic count is <5 mitosis/10 HPF, while YWHAE-HGESS shows mitotic rate > 10 mitoses/10 HPF. Coagulative necrosis is absent in wild tumors and present, together with lymph vascular invasion, in rearranged HGESS [8]. Rearranged HGESS always demonstrates uniform high-grade cytomorphology, although high-grade morphology is not always associated with YWHAE genetic rearrangement [32].

4.3. Immunohistochemistry

Low- and high-grade components of HGESS have a different immunohistochemical profile [8]. The low-grade component, similarly to LGESS, stains positive for CD10, ER, and PR. Cyclin D1 is negative-to-focal in rearranged HGESS, while it is diffusely positive in wild neoplasia. CD117

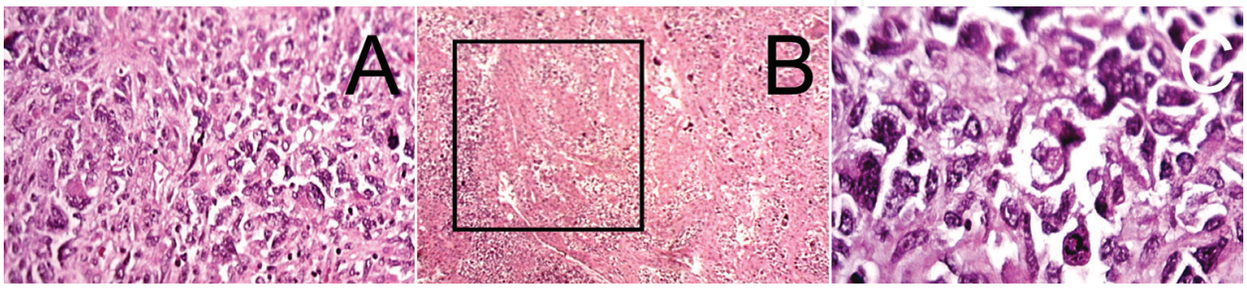

Figure 3. High-grade endometrial stromal sarcoma. (A) High-grade area: proliferation of closely packed large cells with eosinophilic cytoplasms, large nuclei and prominent nucleoli. Cells are arranged in cord pattern, EE, 20×. (B) Delicate and arborized vascular pattern (square), EE, 4×. (C) Pleomorphism and nuclear atypia, 40×.

stains negative [8]. The high-grade component is negative for CD10, ER, and PR in wild tumors and positive in rearranged HGESS [8]. Lack of expression for hormones receptors would have potential treatment implications. CD117 is often positive (**Table 2**) [8]. The different morphological and immunohistochemical features of HGESS may be considered as a surrogate indicator for the underlying genetic rearrangement, even if both fluorescence in situ hybridization (FISH) and reverse transcriptase-PCR (RT-PCR) demonstrated to be more useful [33].

4.4. Differential diagnosis

Adequate sampling is always necessary to diagnose HGESS, since approximately 50% of these tumors contain a low-grade component, which overlaps with LGESS [8]. Low-grade component shows smaller "blue" cells with scanty cytoplasm and smooth nuclear contour, spiral arterioles, infrequent necrosis, positivity for CD10, ER, PR, and negativity for cyclin D1 and c-kit. Moreover, it lacks of biphasic appearance. Differential diagnosis between HGESS and epithelioid LMS should be based on the lacking of a prominent delicate vasculature in the latter. In addition, HGESS does not show a marked atypia. LMS is typically positive for desmin, caldesmon, ER, and PR, but negative (or only focally positive) for cyclin D1 [8]. To differentiate HGESS with intraperitoneal/pelvic locations from GIST, DOG1 antibody is helpful, since it always lack in the former [34].

4.5. Molecular features

As previously shown, genetic fusion YWHAE-FAM22 is characteristic of ESS with high-grade histological features. FISH analysis demonstrated the absolute specificity of YWHAE-FAM22A/B rearrangement in HGESS, since fusion gene has been detected neither in other uterine sarcomas nor in extra-uterine mesenchymal tumors [34]. FISH demonstrated higher sensitivity than RT-PCR in detecting YWHAE-FAM22A/B rearrangement. Croce et al. established that the cut-off of rearranged cells to consider FISH as positive should be 30%; they also recommended to add RT-PCR in borderline cases [35]. Such molecular evidences surely will have diagnostic and therapeutic implications [35].

4.6. Therapeutic approaches

Due to the lack of ER and PR receptors, anti-estrogenic therapy seems to be inappropriate in controlling HGESS growth. Adjuvant CT may provide survival benefit, although experiences are limited [35]. Overexpression of EGFR and Erbb2 has been reported in both HGESS and UUSS. In these cases, treatment with imatinib or trastuzumab may be an option [36]. Recently, overexpression of c-kit has been reported in HGESS carrying the YWHAE/FAM22A/B gene fusion. In these cases, a response to imatinib was also described [36].

4.7. Prognosis

Patient with HGESS typically present with advanced stage disease (stages II–IV). Moreover, in comparison to LGESS, patients with HGESS have earlier (within 1 year after initial surgery) and more frequent recurrences. Particularly, in terms of prognosis, YWHAE-rearranged HGESS is intermediate between LGESS and UUS [37].

4.8. Keypoints

- Myometrial invasion is destructive in HGESS and permeative in LGESS.
- HGESS may morphologically show low- and high-grade areas. Low-grade areas are hypocellular and composed by neoplastic spindle cells, with no nuclear pleomorphism. High-grade areas show round-epithelioid cells.
- Vascular pattern is delicate and arborized.
- It is extremely important to distinguish between rearranged YWHAE HGESS and wild HGESS.
- Mitotic activity in rearranged tumors is <5 mitosis/10 HPF, while it is >10 mitosis/10HPF in wild neoplasia. Coagulative necrosis is absent in the former and present in the latter.
- Mitotic rate should not be used as the unique criterion to distinguish between LGESS and HGESS.
- Distinction between LGESS and HGESS is clinically relevant, since patients with HGESS would have a more aggressive course.
- Cyclin D1 is negative-to-focal in rearranged HGESS and diffusely positive in wild tumors. Immunohistochemistry with CD10 and ER/PR antibodies shows positive results in YWHAE HGESS and negative results in wild HGESS. Due to the lacking of ER/PR receptors, hormonal treatment is not useful in wild neoplasia.
- Because of the frequent positivity for c-kit antibody in both HGESS and GIST, this marker shows low sensitivity. Vice versa, DOG1 is more specific.
- YWHAE-FAM22 fusion gene is characteristic of HGESSs, which show high-grade histological features.

5. Undifferentiated uterine sarcoma (UUS)

In 2014, WHO re-classified gynecological tumors and replaced the old terminology of Undifferentiated Endometrial Sarcoma (UES) with UUS [28]. UUS represents a diagnosis of exclusion, referring to a high-grade sarcoma, which lacks a specific mesenchymal differentiation. UUSs may also enclose poorly differentiated LMS in which smooth muscle cells have been completely replaced by the sarcomatous component [28]. UESs are rare and highly aggressive; they present as intramural mass or intracavitary polyps [8]. Signs and symptoms are non-specific enclosing abnormal uterine bleeding, pelvic mass, or pain due extra-uterine spreads. USS typically occurs in older postmenopausal women [8]. The occurrence of cases with coexisting LGESS component would suggest that USS might also arise from a dedifferentiation of a LGESS [8].

5.1. Macroscopic features

Grossly, cut surface is tan to white, with fleshy consistency. Hemorrhage and necrosis are common [8].

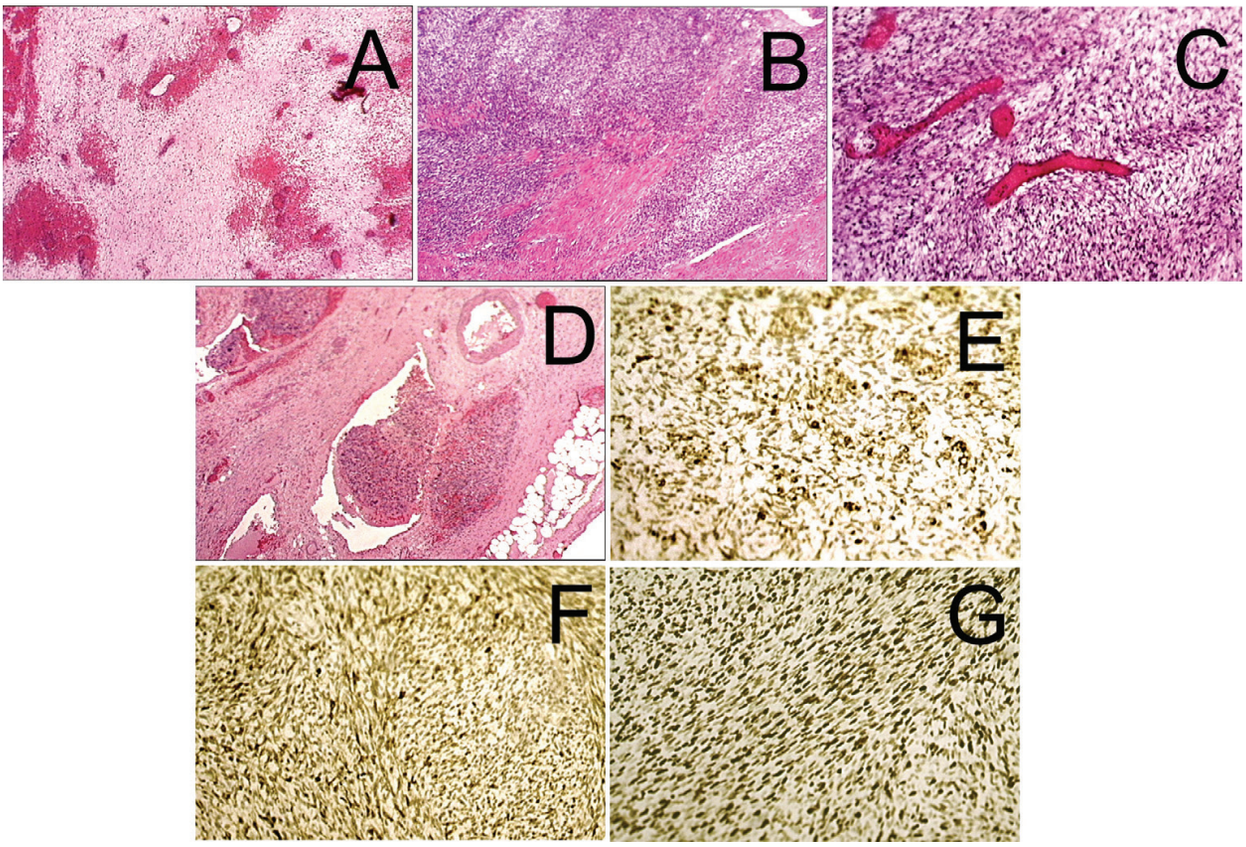

Figure 4. Undifferentiated uterine sarcoma. (A) Tumor-cell necrosis, EE, 4×. (B) Destructive infiltration of the myometrium), EE, 4×. (C) Vascular pattern, EE, 10×. (D) Lymph-vascular invasion with embolism, EE, 20×. (E) CD10 stain, 20×. (F) Desmin stain, 10×. (G) MIB1 index, 10×.

5.2. Microscopic features

UUS shows a combination of severe nuclear atypia, brisk high mitotic rate, and tumor cell necrosis (**Figure 4A**) ([8], p. 1). Histologically, UUS can be distinguished into two histologic variants: uniform UUS (u-UUS) and pleomorphic UUS (p-UUS) [8]. u-UUSs show morphologic and immunophenotypic characteristics of HGESS, and frequently harbor *t(10,17)* rearrangement [38]. p-UUSs show destructive infiltration of the myometrium (**Figure 4B**), highly pleomorphic cells and a fascicular growth pattern not resembling proliferative endometrial stroma [39, 40]. Lymph vascular invasion is common (**Figure 4C** and **D**) [41].

5.3. Immunohistochemistry

Being undifferentiated by definition, the immunohistochemical characterization of UUS it sometimes hard and reflects the heterogenicity of this category of tumors. USSs are typically CD10, p53, and cyclin D1 positive (**Figure 4E**); ER and PR usually stain negative or weakly positive [42]. Desmin, EMA, and keratins may show focal positivity (**Figure 4F**). Smooth muscle actin may be focally positive, although the presence of positive stain for more than one smooth muscle marker should drive to a suspect of LMS [42]. On the other hand, a positive

stain for keratin and EMA should lead to the suspicion of undifferentiated endometrial carcinoma [42]. MIB1 index is usually high (**Figure 4G**).

5.4. Differential diagnosis

Being a diagnosis of exclusion, the suspect of USS should be put after an extensive sampling of the neoplastic mass. Differential diagnosis includes: leiomyosarcoma or rhabdomyosarcoma, which typically show marked cytological atypia and positivity for desmin, h-caldesmon, keratins, and EMA; carcinosarcoma that presents a malignant epithelial component; müllerian adenosarcoma, where benign epithelial cells may be encountered; malignant mixed müllerian tumor, in which the epithelial component is limited [8].

5.5. Molecular features

Genetically, little is known about UUS. In the vast majority of the cases, it has been demonstrated a genetic pathways that is different from those of LGESS and HGESS, although it is not specific (i.e., complex karyotypes, genomic gains, and losses). Particularly, gains of 2q, 4q, 6q, 7p, 9q, 20q and losses of 3q, 10p, and 14q have been detected. A subset of USSs also demonstrated a missense TP53 mutation [15].

5.6. Therapeutic approaches

Patients should be treated with radical hysterectomy and bilateral salpingo-oophorectomy. Adjuvant RT and/or CT are strongly suggested [43].

5.7. Prognosis

Due to their aggressiveness, USSs are associated with a poor prognosis, with an overall survival <2 years [43].

5.8. Keypoints

- USS is a diagnosis of exclusion, lacking of smooth muscle or endometrial stromal differentiation.
- USS diagnosis should be made by extensive sampling of the neoplastic mass, following hysterectomy.
- Histologically, UUS can be distinguished into two histologic variants: uniform UUS and pleomorphic UUS.
- USS is typically CD10, p53, and cyclin D1 positive, while ER and PR are negative or weakly positive. Desmin, EMA, and keratins may show focal positivity.
- USS lacks of a specific molecular pathway, although genetic rearrangements, different from those of LGESSs and HGESSs, have been detected.

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6. Imaging in ESS diagnosis

Even if imaging cannot reliably help to diagnose an ESS before surgery, some specific characteristics can be identified. On US, the neoplastic mass is hypoechogenic, with irregular margins. By Doppler, vascularization pattern appears as irregular. On MRI, ESS typically presents as an invasive endometrial mass with wide myometrial involvement and extension along vessels and/or ligaments. ESS also shows intense 18 FDG uptake. The combination of PET and CT demonstrated to be promising for diagnosis [8]. Due to the high incidence of distant metastases at the first presentation, preoperative imaging of the chest and abdomen may be considered when ESS is suspected [8].

7. Therapeutic approaches

7.1. Surgery

Hysterectomy represents the best practice to treat localized ESS. Since ESS typically expresses ER and PR, there would be a higher risk of recurrence if the ovaries are retained; thus, in postmenopausal women, salpingo-oophorectomy should be performed [8]. Tumor morcellation, a widespread technique used for presumed benign disease, demonstrated to have an adverse impact on patient's outcome [8]. The benefit of lymphadenectomy in ESS is still controversial. The incidence of lymph node metastases is generally low, but it is common in higher stages of disease thus resulting in a worse outcome. Overall, systematic lymphadenectomy does not appear to confer a therapeutic benefit. The role of cytoreductive surgery in locally advanced ESS is controversial. Finally, the resection of distant metastases and cytoreductive procedures should be performed in case of recurrent ESS [27].

7.2. Other therapies

7.2.1. Hormonal therapy

The high rate of positive results for hormones receptors has led to interest in using adjuvant hormonal therapy for both early stage and advanced LGESS. Hormonal therapies are generally well tolerated, even if several questions remain controversial, such as doses, regimens (i.e., progestins, gonadotrophin-releasing hormone agonists, and aromatase inhibitors), and duration of therapy. In general, the lack of significant adverse effects would allow the administration for longer periods. Hormonal therapies seem to be effective for metastatic disease also. Conversely, the frequent lack of ER and PR in HGESS and UUS makes the hormonal therapy ineffective in controlling tumor growth [42].

7.2.2. Chemotherapy

Findings regarding the ESS response to CT are scarce, since data from high-grade and low-grade ESS are pooled. In general, the rate of response to CT is low; thus, it should only be used

when hormonal therapies have become ineffective [42]. Anthracycline and/or ifosfamide are presently considered in the first-line therapeutic regimen [41].

7.2.3. Radiotherapy

Although postoperative RT demonstrated some benefits in controlling loco-regional disease, overall survival is rarely improved, since ESSs typically recur distantly. In recurrent or metastatic ESS, palliative radiotherapy is usually used to reduce symptoms [41].

8. Prognostic factors and survival

JAZF1-LGESSs and LGESSs with no demonstrable genetic rearrangements (wild LGESSs) generally show stage 1 at presentation. Their prognosis is excellent with a low risk of recurrence [41]. In comparison, YWHAE–NUTM2 ESSs typically present in advanced stages (stages 2–4); they frequently recur within a few years after the initial surgery [42].

9. Rare sarcomas

9.1. Rhabdomyosarcoma

It is most common in the uterine cervix than in the uterine corpus. Patients typically presents with abnormal postmenopausal bleeding. Uterine mass is typically polypoid, with a fleshy cut surface and areas of hemorrhage and necrosis. Microscopically, sheets of atypical cells with abundant and eosinophilic cytoplasms, large pleomorphic nuclei, and atypical mitosis are seen. Rhabdomyosarcoma stains positive for muscle specific actin and desmin, but it is negative for smooth muscle actin. Expression of WT1, S100, EMA, and keratins is uncommon. The treatment relies on surgery and CT, with or without RT. Adult age, extracervical location, pleomorphism, depth invasion, and distant metastasis are all bad prognostic factors [8].

9.2. Alveolar soft part sarcoma

It frequently arises in uterine cervix of adolescent and young women. Microscopically, alveolar and organoid patterns separated by delicate fibrovascular septa are seen. Cells show abundant and eosinophilic cytoplasms and contain PAS-positive diastase resisting granules or crystals. Nuclei are large and vesicular, with evident nucleoli. Mitosis is rare. The neoplasia typically shows strong TFE3 positivity. Vimentin, smooth muscle markers, CD10, S100, NSE, and HMB45 may also be positive. Surgery represents the elective treatment [8].

9.3. Angiosarcoma

It presents as a hemorrhagic and diffusely infiltrating mass, often simulating a leiomyoma [8]. Neoplastic cells show vascular differentiation; they stain positive for the vascular endothelial markers CD31, CD34, cyclin D1, and vimentin. The lymphatic endothelial marker D2-40 is absent [8].

9.4. Liposarcoma

The fat cell tumors of the uterus are extremely rare, showing an incidence of 0.03–0.2%. The histogenesis of this tumor is not completely clear. The theory of "tumor metaplasia" has been postulated. Uterine liposarcoma shows an aggressive behavior [8].

10. Conclusions

The in-depth investigations of US biology have certainly improved the therapeutic approaches to these malignancies. Presently, a great number of agents are under investigation. TKI, mTOR inhibitors, growth factors/growth factor receptor inhibitors and antiangiogenic agents, represent the most promising drugs. SARC028 and the anti-PD1 antibody pembrolizumab (also called MK.3475) for advanced sarcomas, and nivolumab plus ipilimumab for patients with unresectable sarcoma, are in phase II trials [43]. Pazopanib (a selective multi-targeted inhibitor of tyrosine kinase receptors), trabectedin, and eribulin have been recently approved. On the other side, immunotherapy did not show potential benefits for US. It is our opinion that future genetic research will significantly allow a better identification of the molecular signatures of US, in order to provide the optimal treatment strategy for these malignancies [43–48].

At the end of the present work, which represents the effort to synthesize all of the updated findings on US, we need to emphasize the importance of interdisciplinary approach to achieve the correct diagnosis and the optimal management for this neoplasia.

The availability of clinical and laboratory information, as well as pharmacological anamnesis, would allow pathologist to put the correct diagnosis of US. Moreover, the continuous research of novel therapeutic approaches would guarantee the updated management of these malignancies.

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