Virchows Archiv (2018) 473:665–678
https://doi.org/10.1007/s00428-018-2470-6

REVIEW AND PERSPECTIVES

Recent advances in the histological and molecular classification of endometrial stromal neoplasms

Joana Ferreira[1,2] · Ana Félix[1,2] · Jochen K. Lennerz[3] · Esther Oliva[3]

Received: 31 July 2018 / Revised: 29 September 2018 / Accepted: 3 October 2018 / Published online: 15 October 2018

Abstract

This review addresses known features and recent developments in the histological, immunohistochemical, and molecular characterization of endometrial stromal neoplasms. We discuss the spectrum of these tumors, from the benign endometrial stromal nodule to low-grade endometrial stromal sarcoma to uterine undifferentiated sarcomas with a special emphasis on the expanding group of high-grade stromal sarcomas, recently added to the 2014 WHO classification, not only discussing the well-established *YWHAE-FAM22* tumors but also two new groups, presenting with *BCOR* alterations including those with *BCOR* tandem internal duplications or *NTRK* fusions. It is likely that this high-grade category of endometrial stromal tumors will expand as increasing molecular data is available.

Keywords Endometrial stromal sarcoma · Uterus · Molecular · Sarcoma · Translocations

Introduction

Endometrial stromal tumors (EST) were first described by Norris and Taylor as a distinct group of mesenchymal neoplasms of the uterus based on their morphological resemblance to endometrial stroma [1]. They classified endometrial stromal sarcomas (ESS) based on mitotic activity into endolymphatic stromal myosis (≤ 10 mitoses/10 HPFs) and stromal sarcoma (> 10 mitoses/10 HPFs) [1]. However, Evans pointed out that marked nuclear pleomorphism but not mitotic activity had an impact on prognosis, labeling tumors with marked cytologic atypia as undifferentiated endometrial sarcomas (UES), typically a diagnosis of exclusion [2]. Numerous attempts to subcategorize ESS based on cytologic features and mitotic index have been attempted with limited success [1–4]. In the largest study to date, Chang and colleagues reported that in tumors confined to the uterus, mitotic activity had no bearing on prognosis [4]. These findings were reflected in the WHO 2003 classification with only two categories of stromal sarcomas being recognized based on cytologic atypia, namely low-grade endometrial stromal sarcoma (LG-ESS) and UES [5]. Later, Kurihara and colleagues reported a third group of ESS characterized by cells with uniform but definite nuclear atypia, permeative myometrial invasion, and a clinical behavior intermediate between LG-ESS and UES [6]. Increasing knowledge on cytogenetics and molecular biology of these high-grade EES led to their reinstitution by the current WHO classification as a distinct group of ESS, known now to be characterized by a t(10;17) leading to the *YWHAE-NUTM2* rearrangement (HG-ESS) [7–9]. Therefore, the current WHO classification acknowledges four categories within the endometrial stromal family of tumors: endometrial stromal nodule, LG-ESS, high-grade endometrial stromal sarcoma, and undifferentiated uterine sarcoma [9].

This review intends to briefly summarize the morphologic and immunohistochemical features of the well-known categories of endometrial stromal neoplasms and highlight the most relevant discoveries related to the molecular classification of endometrial stromal neoplasms with a special emphasis on HG-ESS (Table 1).

✉ Joana Ferreira
joanaferreira@gmail.com

[1] Serviço de Anatomia Patológica, Instituto Português de Oncologia de Lisboa Francisco Gentil, Rua Prof.Lima Basto, 1099-023 Lisbon, Portugal

[2] Faculdade de Ciências Médicas da Universidade Nova de Lisboa (CEDOC), Lisbon, Portugal

[3] Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Table 1 Main morphological, immunohistochemical, and molecular features of endometrial stromal tumors

Main molecular subtypes	ESN/LG-ESS		HG-ESS		UUS
	JAZF1-SUZ12	Non-JAZF1 related	YWHAE	BCOR*	Not-described
Morphology	- Oval cells with no atypia concentrically arranged around arborizing vessels - LG-ESS vs. ESN: LVI+ or ≥3 foci ≥3 mm of permeative growth into myometrium	PHF1-related tumors: sex cord-like differentiation	- Permeative or destructive growth - Necrosis - Round, monotonous cells with increased N/C ratio and > 10mit/10HPF - 50%: accompanying histologically low-grade component ~ LG-ESS	- Permeative growth - Spindle cells in myxoid stroma, often with brisk mitotic activity	- Diagnosis of exclusion - Destructive, sheet-like growth - Pleomorphic cells with focal rhabdoid features - Frequent necrosis and mitoses, including atypical ones
IHC	CD10+, ER+, PR+, WT1+		HG component: cyclin D1+, CD117+, BCOR+, ER, PR and CD10-LG-component: CD10+, ER+, PR+	CD10+, cyclin D1, and BCOR+, ER+/−, PR+/, SMA+/−, desmin+/−	p53+, ER−, PR−, CD10+/−
Molecular alterations	JAZF1-SUZ12	PHF1-JAZF1; PHF1-EPC1, PHF1-BRD8, MEAF6-PHF1, MBDT-Cxorf67	YWHAE-NUT2M	ZC3H7B-BCOR, BCOR- ZC3H7B, BCOR exon 16 ITD	TP53 missense mutations

EST—endometrial stromal nodule, LG-ESS—low-grade endometrial stromal sarcoma, HG-ESS—high-grade endometrial stromal sarcoma, UUS—uterine undifferentiated sarcoma, LVI—lymphovascular invasion, mit—mitoses, IHC—immunohistochemistry, HG—high grade, LG—low grade, ER—estrogen receptor, PR—progesterone receptor, SMA—smooth muscle actin, ITD—internal tandem duplication

Endometrial stromal nodule and low-grade endometrial stromal sarcoma

Endometrial stromal nodule and LG-ESS share morphological, immunohistochemical, and molecular features. As both tumors display uniform small cells with scant cytoplasm and oval nuclei reminiscent of proliferative phase endometrial stroma that sometime whorl around arterioles, distinction is based on the finding(s) of myometrial infiltration and/or lymphovascular invasion [1, 9, 10]. Endometrial stromal nodule is typically seen on gross examination as a well circumscribed yellow to tan often polypoid endometrial mass (rarely intramyometrial or subserosal) [10, 11]. On microscopic examination, it is also well circumscribed but may have finger-like projections into the myometrium, typically ≤3, each measuring < 3 mm in greatest extent [9, 10]. The presence of lymphovascular invasion excludes this diagnosis [9]. In contrast, LG-ESS often shows yellow to brown coalescent nodules and "worm-like" plugs of tumor infiltrating the myometrium as well as myometrial and parametrial veins (Fig. 1a) [9]. In some instances, distinction between these two entities is not easy and extensive sampling may be required with some tumors showing very limited (albeit more than allowed in ESN) myometrial invasion (EST with limited infiltration) [11]. There is scarce and conflicting information in the literature regarding the behavior of this subgroup of EST. In the two reported cases with available follow-up, one patient was alive and well after 62 months [11]. In the other report, they describe a very small (0.7 cm) tumor with apparent complete sampling of the myometrial interface, where a lymphovascular invasion was detected in the right pelvic soft tissues in the staging surgery [12]. Despite this, the patient was alive and well after 13 months [12]. Thus, more studies on ESTs with limited infiltration are needed, although it may be difficult due to the rarity of this scenario. In hysteroscopic or morcellated specimens, even though careful gross evaluation of fragments should be performed, when myometrial invasion is not overt as often seen in ESS, certainty on the tumor myometrium interface and thus infiltration may be limited. In such scenario, a diagnosis of EST with a comment stating that the distinction between a ESN and a LG-ESS with minimal infiltration cannot be made is reasonable.

Other morphologic features that can be seen in both tumors include arterioles, sometimes hyalinized, resembling those seen in proliferative-phase endometrium (characteristic but infrequently striking), foamy histiocytes, and hyaline plaques (Fig. 1b). Areas of stromal hyalinization may be seen [4, 9, 10]. Smooth muscle metaplasia (most commonly seen as

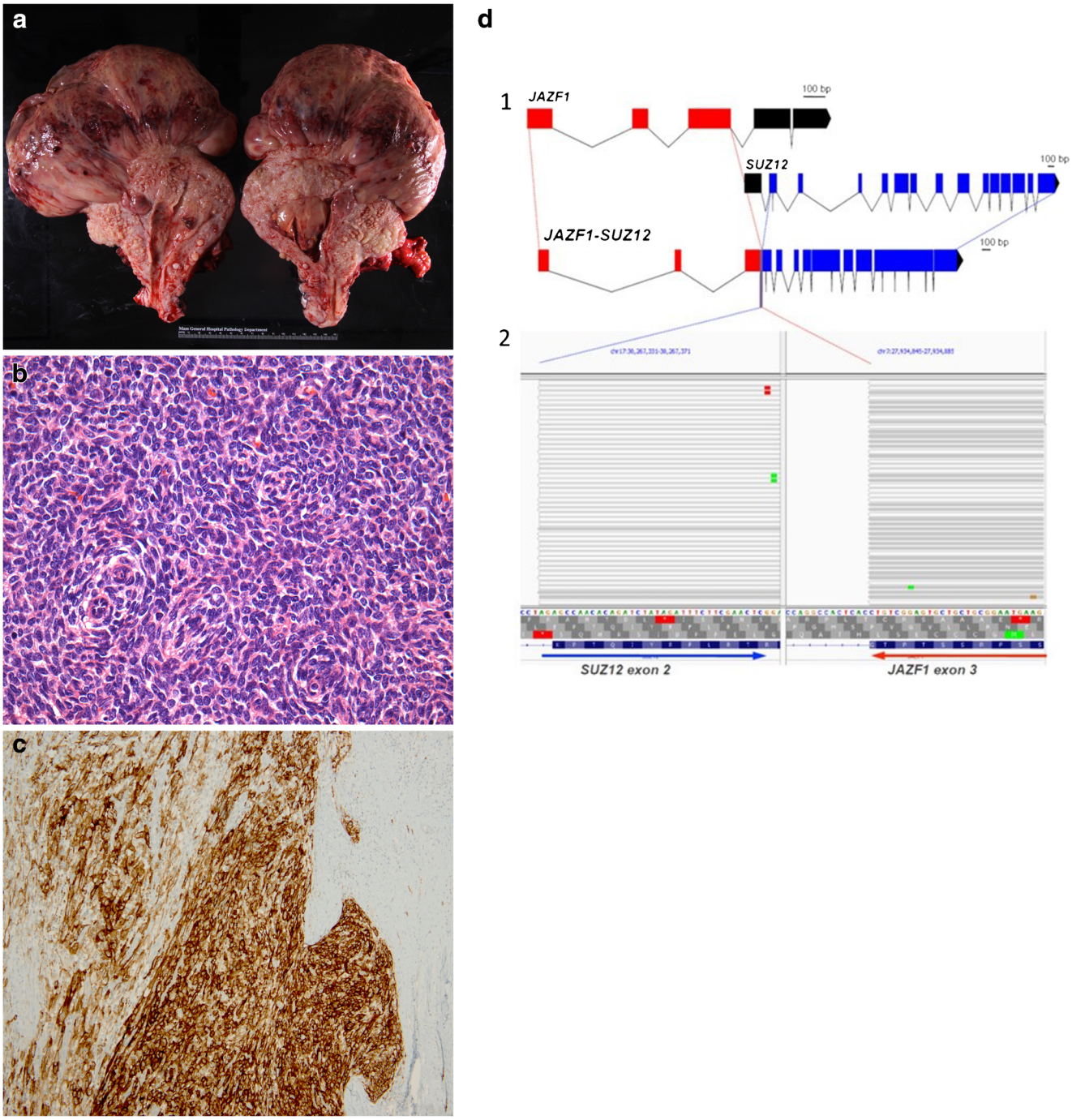

Fig. 1 Low-grade endometrial stromal sarcoma. **a** On gross examination, the tumor has an intracavitary tan to yellow polypoid component, extensive myometrial permeation as worm-like plugs of tumor, as well as massive extrauterine extension. **b** Small, round, monotonous cells with a diffuse growth that whorl around small vessels are characteristic of this tumor and reminiscent of proliferative-phase endometrial stroma. **c** The tumor cells are typically strongly and extensively CD10 positive. **d** 1. The chromosomal translocation t(7;17) (most common in these tumors) results in a chimeric transcript containing the first three (red) of five total exons of the JAZF1 gene (chromosome 7) fused with the 15 exons (blue) of the SUZ12 gene (chromosome 17). 2. Integrative Genome Viewer (V2.4.10.03) screenshot of the JAZF1-SUZ12 gene fusion depicts numerous split JAZF1 (exon3) to SUZ12 (exon 2) reads; note that JAZF1 is encoded on the minus strand

starburst pattern) [11, 13–22], myxoid/fibromyxoid change [11, 17, 23–27], sex cord-like differentiation (Fig. 2a) [10, 11, 16, 20, 21, 23, 28–32], endometrioid-type glands [22, 33–35], adipocytic [18] and skeletal muscle differentiation [18, 21, 36], pseudopapillae [37], rhabdoid cells [20, 23, 38], or cells with granular eosinophilic epithelioid [39] or clear cytoplasm [40], and osteoclast-like cells [19] or cells with bizarre nuclei [18] have also been reported.

Tumor cells characteristically express CD10 (Fig. 1c), ER, PR, and WT1 [41–44]. Smooth muscle actin is also commonly positive [14, 42]. Desmin and caldesmon can be positive, more commonly the former in both endometrial stromal cells and areas with smooth muscle differentiation [14, 41, 45]. Over 70% of tumors are positive for androgen receptors [46], and some investigators have shown nuclear β-catenin positivity [6, 47]. Variable degree of keratin expression may be seen. [11, 48, 49] Areas of sex cord differentiation may be positive for inhibin, calretinin, CD99, melanA, and WT1 [50–52], but also for keratins and smooth muscle markers [29, 30]. IFITM1, a novel endometrial stromal marker reported to be positive in the majority of these tumors, has been stated to better discriminate between low-grade endometrial stromal and smooth muscle tumors when compared to CD10; however, more experience is needed to validate these results [53]. BCOR, cyclin D1, KIT, and DOG1 are typically negative, although focal cyclin D1 and c-kit positivity may be seen [54–60].

Molecular genetic studies have shown recurrent chromosomal translocations involving most frequently t(7;17)(p15;q21) resulting in a *JAZF1-SUZ12* fusion transcript (Fig. 1d) [61–63]. Other reported molecular alterations include t(6;7)(p21;q21), t(6;10;10)(p21;q22;p12), t(1;6)(p34;p21), t(5;6)(q31;p21), and t(X;17), corresponding respectively to *PHF1-JAZF1*, *PHF1-EPC1*, *MEAF6-PHF1*, *PHF1-BRD8*, and *MBTD-CXorf67* fusions [64–68]. The t(7;17)(p15;q21) leading to a *JAZF1-SUZ12* fusion transcript is the most common reported rearrangement, estimated to be present in ~ 50% of LG-ESS and ~ 65% of endometrial stromal nodules and in a small percentage of undifferentiated uterine sarcomas (likely those that originate from low-grade tumors) [6, 63, 64, 69–77]. Although both JAZF1 and SUZ12 mRNA is expressed at low levels in normal endometrium, it appears to derive from RNA trans-splicing and only be present in a transient from during part of the cycle [78]. However, JAZF1-SUZ12 fusion is specific of endometrial stromal nodules and low-grade ESS among mesenchymal tumors of the uterus, but it appears to be less common among variants including smooth muscle, fibromyxoid, sex cord-like and epithelioid morphology [63, 79]. *JAZF1* has also been shown to rearrange with the PHD finger 1 protein gene (*PHF1*) from 6p21 [64]. The *PHF1* gene itself has been found to be involved in rearrangements with other partners in LG-ESS including: *EPC* (10p11), *MEAF6* (1p34), and *BRD8* (5q31.2) [64–66, 68]. Yet, another rearrangement t(X;17) resulting in *MBTD1-CXorf67* fusion has been also identified [67].

JAZF1, SUZ12, PHF1, and MBDT1 are members of the polycomb group protein family also involved in transcriptional repression [80]. The oncoproteins that result from *JAZF1-SUZ12* and *JAZ-PHF1* genetic fusions are believed to cause transcriptional dysregulation [64, 81]. *EPC1* is part of the nucleosome acetyltransferase of histone H4 complex whereas *MEAF6* is part of histone acetyltransferase multi-subunit complexes. The fusion proteins EPC1-PHF1 and MEAF6-PHF1 alter acetylation patterns of histone proteins, which lead to unraveling of the heterochromatin and aberrant gene expression [66, 80]. It appears that benign and low grade ESTs share genes that are known to be involved in transcriptional regulation. Despite being different, all these gene fusions appear to represent biologically and clinically equivalent oncogenic events in the tumorigenesis of this group of tumors [80]. In general, specific translocations do not correlate with specific morphology except for ESS with sex cord-like differentiation found to harbor more commonly alterations in the *PHF1* gene in one study (Fig. 2b) [76]; however, these findings were not confirmed in another study [71]. Tumors with *PHF1* alterations not infrequently are also associated with smooth muscle metaplasia [76].

Of interest, *PHF1*-related fusions involving various partners including *EP400*, *MEAF6*, and *EPC1* have been reported in ossifying fibromyxoid tumors, which are rare soft tissue neoplasms with an intermediate risk of malignancy [82–85]. Morphologically, these are multinodular, well-circumscribed neoplasms with uniform to round desmin and S100 protein positive cells arranged in cords and nests set in a fibromyxoid stroma, an appearance that vaguely overlaps with some ESTs [83, 86]. One cardiac sarcoma likely representing an ossifying fibromyxoid tumor has also been reported to carry a *JAZF1-PHF1* rearrangement [87]. *ZC3H7B-BCOR*, *CREBBP-BCORL1*, and *KDM2A-WWTR1* fusions have also been reported in these tumors highlighting a significant genetic overlap with ESTs [83, 88].

Rarely, LG-EES harboring *JAZF1* translocations have been described to be associated with high-grade areas with a faster progression [89], while some low-grade tumors, with either conventional or variant (fibromyxoid) morphology and t(10,17), have been reported associated with YWHAE rearrangement [90, 91]. Micci and colleagues have shown by microarray analysis a large number of genes to be differentially expressed between EES harboring *JAZF1-SUZ12* fusion and those without it [80]. In the same study, genes known to be implicated in acute myeloid leukemia (*CREBBP* and *MLLT4*) were also noted to be present for the first time in a LG-ESS by next generation sequencing [80]. These findings suggest that the number of ESS-associated genes is likely to increase in the future [80].

As ESN are benign tumors, they are appropriately treated by hysterectomy. In hysteroscopic or morcellated specimens, where the complete myometrial interface cannot be evaluated, hysterectomy should ensue. In women of reproductive age who desire to preserve fertility, adjuvant hormonal therapy together with follow-up diagnostic imaging and hysteroscopy is a potential option [92–94]. Most patients with LG-ESS present with stage I disease and have an excellent prognosis with an overall five-year survival exceeding 90%; however, it

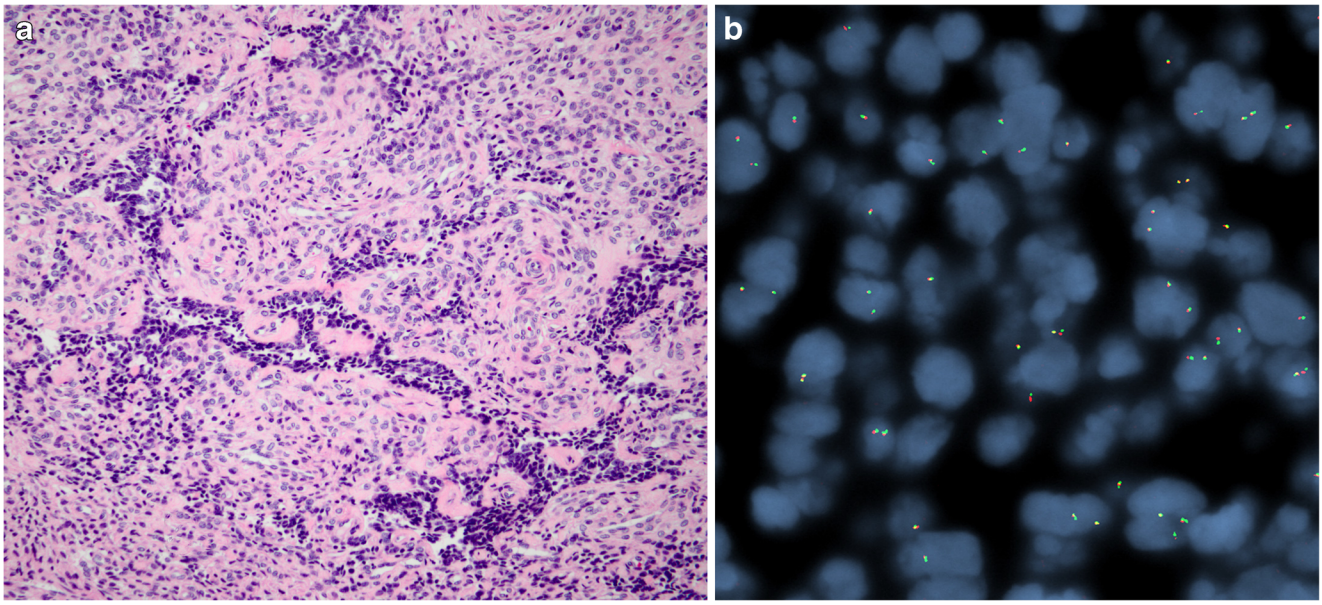

Fig. 2 Low-grade endometrial stromal tumors with sex-cord areas (**a**). Tumors with this morphology have been reported to carry more frequently PHF1 rearrangements (**b**)

is much lower in patients with stage II-IV tumors [4]. Total hysterectomy and bilateral salpingooophorectomy, with or without adjuvant therapy, are the treatment of choice [8, 95–97], although hormone therapy including aromatase inhibitors or radiation therapy may be alternative options [95–97]. Relapses which can occur long after the initial diagnosis respond to anti-estrogen therapy [95, 98, 99].

High-grade endometrial stromal sarcomas

In the current WHO classification, high-grade endometrial sarcomas are solely represented by those harboring t(10;17) rearrangement leading to the *YWHAE-NUTM2* fusion protein [7–9]. Recent evidence has shown that endometrial sarcomas harboring other genetic alterations namely in the *BCOR* gene including those with BCOR tandem internal duplications are also associated with a prognosis that is worse than LG-ESS but better than UES and thus, should be classified as HG-ESS [100–103]. However, other subsets of HG-ESS likely exist, including those arising from dedifferentiation in *JAZF1*-related ESS, potentially some within the category of tumors with NTRK fusions or others yet to be unveiled [103].

YWHAE-NUTM2 ESS

Patients with *YWHAE-NUTM2* HG-ESS frequently present with advanced stage disease when compared to LG-ESS and are associated with frequent recurrences [8, 104]. On gross examination, tumors have a fleshy cut surface with common areas of necrosis and/or hemorrhage. Morphologically, they show either a destructive or permeative growth and uniform morphology at low-power magnification. Tumors are composed of round "blue" cells with high nuclear to cytoplasmic ratio, nucleomegaly (4–6 times the size of a stromal lymphocyte nuclei), slightly irregular or angulated nuclear contours without prominent nucleoli but typically with brisk mitotic activity (> 10/10 HPFs) associated with a rich but delicate arborizing capillary network (Fig. 3a) [8]. Focal pseudoglandular or rosette-like morphology as well as sex-cord like differentiation have been occasionally described [6, 8, 105]. In approximately half of the tumors, a low-grade component with fibroblastic/myxoid or much less commonly classic morphology can be found, imparting a biphasic appearance [6, 8, 104]. These low-grade and high-grade areas may or not be well-demarcated from each other [8]. However, there is increasing evidence of the morphologic heterogeneity of these neoplasms as recently it has been reported a *YWHAE* rearranged ESS with pure low-grade morphology in the primary uterine tumor that when progressed displayed fibroblastic as well as large atypical cells which eventually progressed to HG-ESS [90].

High- and low-grade components typically have opposite immunohistochemical profiles. The high-grade areas are diffusely (> 70% of cells) and strongly positive for cyclin D1 (Fig. 3b) [54, 106]. It has been stated that in the setting of a uterine mesenchymal neoplasm, sensitivity, and specificity of this antibody for the diagnosis of *YWHAE*, rearranged ESS is very high (100 and 99%, respectively) [104]. Rare tumors with diffuse cyclin D1 positivity lacking t(10;17) likely represent BCOR-related HG-ESS (see below) or HG-ESS with undiscovered genetic changes, while tumors that may only be weakly cyclin D1 positive or show positivity in < 70% of cells can still have a gene fusion confirmed by FISH [60, 101, 102, 104]. It is also important to keep in mind that rarely other tumors including undifferentiated uterine sarcoma, leiomyosarcoma, Ewing

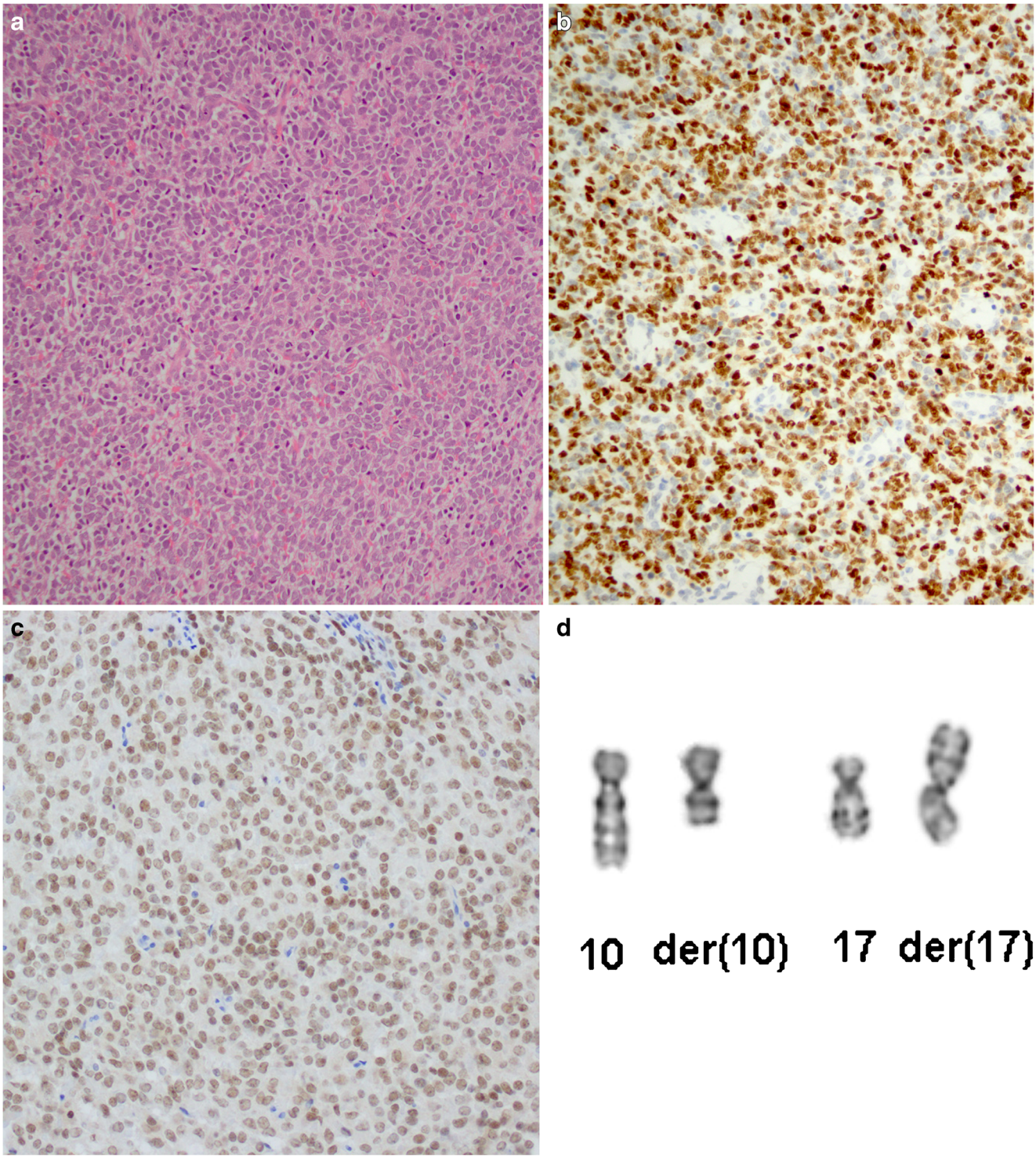

Fig. 3 High-grade *YWHAE-NUT2M* rearranged endometrial stromal sarcoma. **a** A diffuse or vaguely nested pattern of cells with high nuclear to cytoplasmic ratio with round to angulated nuclei accompanied by brisk mitotic activity is characteristic of these tumors. Notice the delicate sinusoidal vasculature. **b** The tumor cells are typically diffusely and strongly positive for CyclinD1 but negative for CD10, ER, and PR. **c** These tumors are also positive for BCOR. **d** G-banded partial karyotype showing a balanced translocation, t(10;17). Courtesy of Paola dal Cin, PhD, Brigham, and Women's Hospital, Boston, MA, USA

sarcoma, and undifferentiated endometrial carcinoma may be strongly positive for this marker [60, 104, 107]. CD117 is also characteristically positive in the high-grade component and can show focal positivity in the low-grade areas [108]. However, no *KIT* mutations have been detected in these tumors and DOG1 is typically negative in both components [108]. Recently, diffuse

and strong BCOR immunostaining has been detected in this high-grade component of *YWHAE*-rearranged sarcomas (Fig. 3c) [60]. This marker may be especially useful in tumors with variant morphology or with typical morphology with minimal or absent cyclin D1 expression, and it has been stated that it is more reliable than cyclin D1 in the identification of this high-grade component [60]. Weak BCOR expression may be rarely encountered in endometrial stromal nodules and low-grade ESS and more frequently and of weak to moderate intensity in leiomyosarcomas [60]. CD99 has been reported to be positive in one tumor [105]. CD10, ER, and PR are negative, while p53 immunoreactivity is typically wild type [6, 104]. In contrast, the low-grade component is typically CD10, ER, and PR positive and lacks cyclin D1 expression but may show variable BCOR positivity [6, 54, 60].

The t(10;17) was initially reported in clear cell sarcomas of the kidney and only later discovered in ESS (Fig. 3d) [7, 8, 109]. This translocation leads to the fusion between YWHAE and either of two nearly identical NUTM2 proteins (NUTM2A or NUTM2B) resulting in a YWHAE-NUTM2 fusion oncoprotein [7]. Both FISH and RT-PCR have been used to detect *YWHAE-NUT2M* rearrangement although FISH is more commonly used [8, 77, 104]. It is important to keep in mind that *YWHAE-NUT2M* and *JAZF1/SUZ12/EPC1/PHF1* rearrangements are mutually exclusive [8]. Of note, *YWHAE*, *NUTM2A*, and *NUTM2B* rearrangements have been shown by FISH in a uterine angiosarcoma, but no *YHWAE-NUTM2* fusion transcript was identified by RT-PCR [110].

Prognosis of patients with this HG-ESS seems to be intermediate between LG-ESS and UES [8, 111]. Five-year survival is achieved in nearly 33% of patients with a median survival of 20 months, but disease control and long survivals have also be reported even in metastatic settings [8, 96, 111, 112]. Surgery and adjuvant chemotherapy, especially anthracycline-based regimens, and/or radiation therapy remain the treatment of choice [95, 112].

BCOR-related ESS

Recently, a new group of ESS harboring *BCOR* alterations have been described comprising both *ZC3H7B-BCOR* rearranged tumors and those with internal tandem duplications (ITD) in the last exons of the *BCOR* gene [60, 100–102]. These neoplasms often display high-grade morphologic features and available albeit limited clinical data suggests that they behave more aggressively than LG-ESS; thus, they have been placed within the HG-ESS category [60, 100–102].

Seventeen patients with ESS carrying the *ZC3H7B-BCOR* fusion have been reported [100, 101]. Median age at diagnosis was 54 (range 28–71) years. Seven (41%), three (18%), and seven (41%) presented with FIGO stage I, II, and III disease, respectively. Two of the five patients who underwent lymph node sampling had lymph node metastases. Clinical follow-up data was available for five of these patients, two with stage III and three with stage I disease. All patients developed recurrences and four (including all stage I patients) died of disease. Tumors ranged in size from 1.5 to 12 (median, 9.7) cm and five were polypoid. They frequently involved both endometrium and myometrium (11/13) and showed either a broad front pattern of invasion, a tongue-like infiltrative pattern (typical of LG-ESS), or both. They were composed of spindle cells arranged in haphazard fascicles sometimes often embedded in a myxoid stroma that ranged from focal to abundant, sometimes forming lakes (Fig. 4a, b). Spindle cells had ovoid to spindle nuclei with even chromatin and no significant pleomorphism in all but one case. Collagen plaques were observed in ~ 50%. Most tumors (14/17) had a mitotic rate ≥ 10/10 HPF, but it ranged from 1 to 50/10 HPF. Necrosis, mostly of infarct-type, was seen in 10/17 tumors.

In contrast to HG-ESS with t(10,17), these tumors typically show diffuse positivity for CD10 (although it may be weak/focal) and may display focal staining for one myogenic marker (SMA>>>>desmin or caldesmon). ER and PR are variably expressed. Cyclin D1 is typically strong and diffuse (> 95% cells) in most tumors, while diffuse BCOR expression (> 95 cells) has been noted in half of them (all but one strong) Fig. 4c). All 17 tumors tested in the largest study to date harbored *ZC3H7B-BCOR* gene fusions by next-generation sequencing or FISH analysis (Fig. 4d) [100, 101]. The *ZC3H7B-BCOR* gene fusion had been previously reported in ESS by Panagopoulos and Micci in two separate studies [80, 113]. Tumors reported were CD10 positive and occurred in patients who presented with high-stage disease [113]. No morphological or clinical details were available on the case reported by Micci [80]. Furthermore, previous karyotypic data reported in two ESS showed t(X;22) likely to correspond to ZC3H7B-BCOR fusion; however, no further morphological details were available on these cases either [7].

A total of four ESS harboring ITDs involving *BCOR* (*BCOR* ITD) have been recently reported by two groups [60, 102]. They were identified through genomic PCR and targeted sequencing. *BCOR* ITD involved exon 15 (in three) and exon 16 (in one)(Fig. 5a) [60, 102]. Despite the small number of cases reported so far, they typically appear to occur in younger patients (ages 18, 22, 25, and 32) when compared to *BCOR*-rearranged tumors but seem to share with the latter, a similar morphology (although they may also be epithelioid) (Fig. 5a) and clinical course. In three, both permeative and destructive growth patterns were observed and in the remaining, only a tongue-like pattern of myometrial invasion was noted. In all but one tumor, a distinct myxoid stroma was observed whereas in the latter, stroma was collagenous. All neoplasms had spindle and round cells and three of them displayed cytological atypia. Lymphovascular invasion was noted in three out of four tumors in which this feature was evaluated [60, 102]. Follow-up was available in two patients

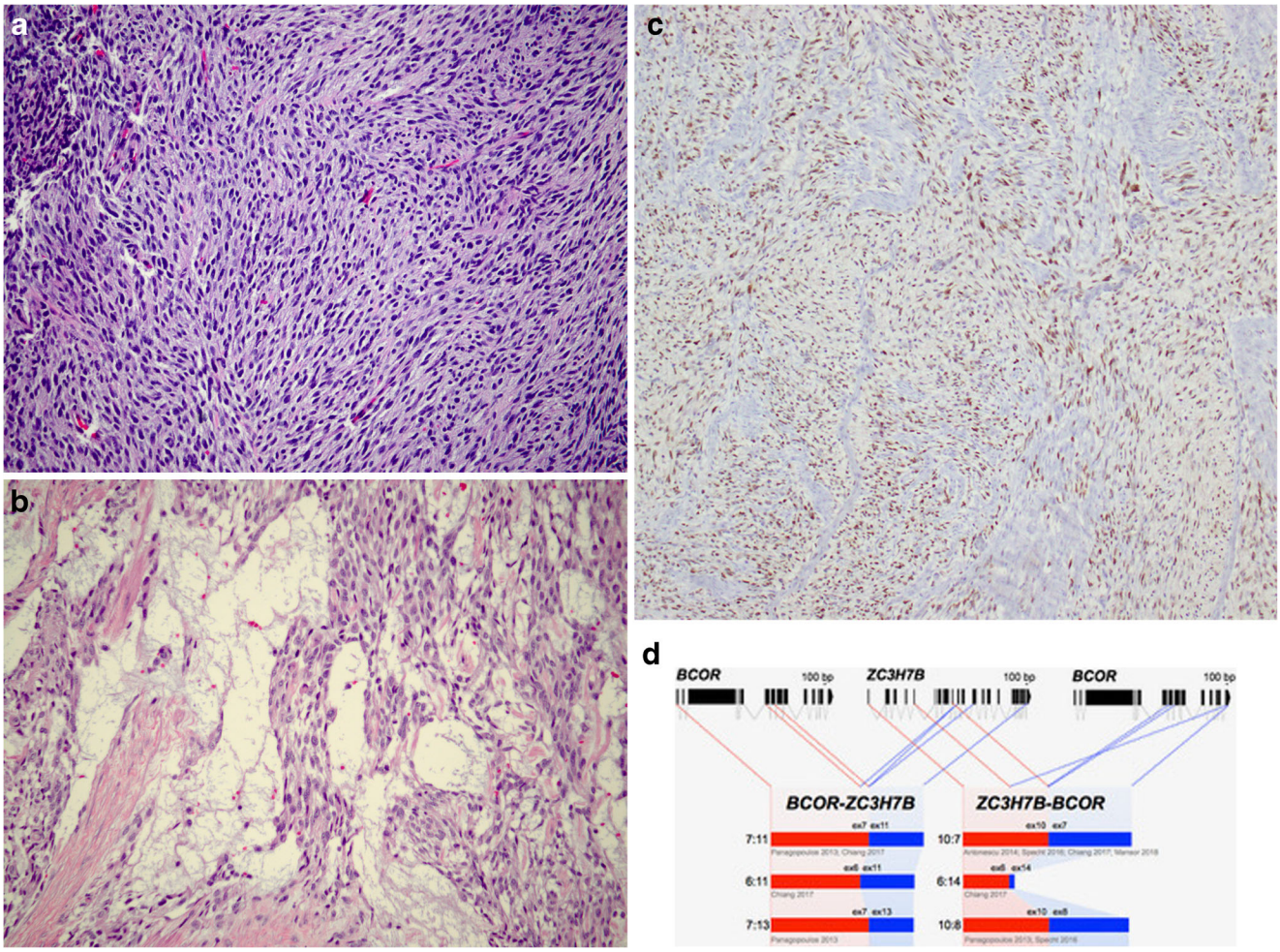

Fig. 4 BCOR rearranged high-grade endometrial stromal sarcoma. **a** The tumors often have a fascicular growth of spindle cells with oval nuclei with little pleomorphism and variable amounts of cytoplasm. **b** Myxoid stroma is common and can be abundant and may form lakes. **c** Neoplastic cells show diffuse reactivity for BCOR, although often of variable intensity. **d** Schematic representation of the fusion gene transcripts involving *BCOR* and *ZC3H7B*. To account for reciprocal fusions (with either ZC3H7B in 5′ position vs. BCOR in 5′ position), the various reported exon structures are provided along with the relevant publication (note: some prior publications refer to "ossifying fibromyxoid tumors")

even though stage was not mentioned in any of them; one died of recurrent disease 8 years and the other had no evidence of disease 22 years after diagnosis and anthracycline-based chemotherapy. All tumors display strong and diffuse cyclin D1 and BCOR positivity, with focal CD10 positivity in three [60, 102]. Focal desmin positivity was noted in one tumor (myogenic markers reported in three) [102]. ER and PR, reported in one tumor, were negative [60].

BCOR-related ESS share morphological and immunohistochemical features with myxoid leiomyosarcomas including spindled cells with myxoid background as well as positivity for CD10 and muscle markers and rarely diffuse cyclin D1 positivity in leiomyosarcomas. In fact, some myxoid leiomyosarcomas reported in the literature may likely represent BCOR-related ESS [60, 100, 114]. BCOR appears to be a sensitive marker in identifying YWHAE-rearranged sarcomas but weak to moderate BCOR positivity may be seen in ~ 20% of leiomyosarcomas and ~ 6% of LG-ESS; thus, it is important to use a panel of antibodies as well as extensive sampling to help to reach the correct diagnosis. [60, 100–102] Of note, ~ 25% of myxoid leiomyosarcomas show PLAG1 rearrangements, not reported so far in ESS [115].

Recently, a *JAZF1-BCORL1*-ESS initially diagnosed as a LG-ESS has also been reported and although no morphological description is provided, available pictures show in our opinion high-grade morphology. The tumor underwent an aggressive clinical course indicating that this rearrangement may also be seen in HG-ESS [116].

BCOR is a transcriptional corepressor involved in suppressing gene expression by either interacting with BCL6 or binding to PCGF1 as part of polycomb repressive complex 1 (PRC1) and inducing gene silencing by histone modification [117–121]. Germline *BCOR* loss of function mutations result in X-linked oculofaciocardiodental (OFCD) syndrome and

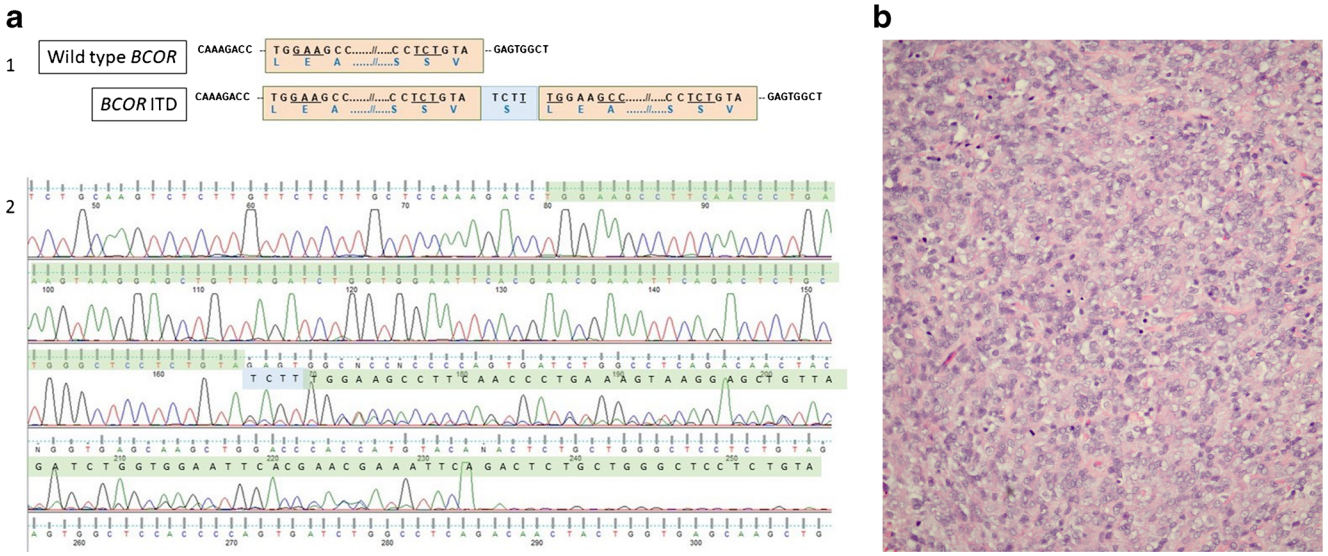

Fig. 5 High-grade BCOR-ITD endometrial stromal sarcoma. **a** BCOR exon 16 internal tandem duplication in high-grade endometrial stromal sarcoma. (1) Schematic demonstrating wild type BCOR (top) and BCOR internal tandem duplication (bottom) sequences. (2) Duplicated region (highlighted in beige) overlapping with the BCOR wild type sequence with a 4-bp insertion (highlighted in blue) in between duplicated regions. Courtesy of Cristina Antonescu, MD, Memorial Sloan Kettering Cancer Center, New York, NY, USA. **b** The tumor is composed of round to oval cells in a slightly myxoid background with thin vessels

Lenz microphthalmia [122]. *BCOR* rearrangements and inactivating mutations have been reported in various hematological and solid human cancers including acute myeloid leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, medulloblastomas, retinoblastoma, hepatocellular carcinoma, soft tissue and bone round cell sarcomas, and CNS neoplasms [88, 123, 124]. *ZC3H7B* (ZC3H7B-BCOR) is involved in protein-nucleic acid interactions [80]. Of interest, ZC3H7B-BCOR rearrangement has also been described in ossifying fibromyxoid tumors, where rearrangements described in LG-ESS (*MEAF6-PHF1*, *EPC1-PHF1*) have also been described while *BCOR* ITD has been reported in tumors where *YWHAE-NUTM2B/E* fusions are also frequent including clear cell sarcoma of the kidney, undifferentiated round cell sarcoma of infancy, and primitive myxoid mesenchymal tumor of infancy [83, 109, 117, 125, 126]. These tumors also share morphologic features, upregulation of *BCOR* mRNA, overlapping gene signatures, and BCOR expression by immunohistochemistry [117, 127].

Little is known about the natural course and optimal treatment of BCOR-related ESS [60, 100–102]. The available clinical data suggests that most patients present with advanced stage tumors have local relapses as well as lymph node and distant metastases and respond poorly to adjuvant therapy [60, 101, 102].

Other high-grade ESS (dedifferentiated LG-ESS)

Rarely, conventional LG-ESS may be seen in association with a high-grade/undifferentiated sarcoma [6, 89, 128, 129], but these tumors are classified in the current WHO as undifferentiated uterine sarcomas [9]. In contrast to classical LG-ESS, they have a destructive pattern of invasion although permeative areas more reminiscent of LG-ESS can also be recognized [6, 89]. The high-grade component displays large epithelioid cells with nucleomegaly, prominent nucleoli, high mitotic index, and necrosis [6, 89]. In tumors tested, CD10 was often positive in the low-grade component but variably positive or negative in the high-grade areas. Reports concerning ER and PR have shown inconsistent results [89, 129, 130].

There are very few molecularly confirmed ESS with JAZF1-SUZ12 genetic fusion with high-grade features [6, 63]. One of them was a purely high-grade sarcoma classified as an UES [63]. The other contained classic low-grade ESS juxtaposed to a monomorphic high-grade sarcoma (70 mitoses/10 HPF) [6]. Gene expression studies have identified 514 differentially expressed genes between high-grade not otherwise specified and low-grade ESS [80]. Several investigators have also reported that chromosomal aberrations differ considerably between these two groups [80, 131], suggesting that they correspond indeed to different pathological entities and that tumor progression from one to the other is very unlikely [80].

Undifferentiated uterine sarcomas

Undifferentiated uterine sarcomas are high-grade sarcomas that lack specific lines of mesenchymal differentiation and include tumors arising in the endometrium and myometrium, thus the change in the nomenclature in the most recent WHO classification. All other uterine sarcomas as well as poorly

differentiated and undifferentiated carcinomas and malignant mixed Müllerian tumors must be ruled out before a diagnosis of UUS is rendered. No recurrent genetic fusions have been described in this group of tumors [9].

In 2008, Kurihara et al. proposed a classification system for UES based on the degree of nuclear pleomorphism delineating two groups with different prognosis: uniform and pleomorphic UES [6]. Overexpression of cyclin D1 was a frequent event in the uniform UES group and this finding was later found to correlate with the YWHAE-FAM22 translocation, raising strong evidence that this group of tumors represented in fact YWHAE-FAM22 sarcomas [106]. The other group of tumors displayed overt pleomorphism growing in a destructive, sheet-like fashion [6]. These morphological findings were later confirmed and expanded by other groups [89, 132]. These tumors are frequently ER and PR negative [89, 132], while CD10 expression is variable with only a small number of cases tested [87]. Cyclin D1 has been reported to be positive in a few tumors but never showing the diffuse and strong staining seen in YWHAE-FAM22 or BCOR related tumors [89, 132]. Aberrant expression of p53 and *TP53* gene missense mutations have been reported in 32–50% [6, 132]. Chromosomal alterations in the UES have been found to be heterogeneous, and complex karyotypes have been reported [133, 134]. There appears to be no accumulation of aberrations from LG-ESS to UES as also observed when comparing LG-ESS to HG-ESS [133].

These neoplasms are typically associated with poor outcomes, although a few patients with long survival have been reported [132, 135, 136]. Recently, two different groups have suggested that a mitotic count > 25/10 HPF is the most reliable prognostic discriminator in these group tumors [132, 136]. Surgical treatment is recommended, but the value and choice of adjuvant therapy are yet to be determined [95].

Very recently, a new uterine sarcoma subtype with features of fibrosarcoma harboring *NTRK* fusions has been described to arise in the uterus. All four tumors presented in premenopausal women and three arose in the cervix. All tumors shared the finding of monomorphic spindle cells typically with focal and moderate nuclear pleomorphism as well as brisk mitotic activity. Focal SMA and S100 expression was seen in all tumors but desmin, ER, PR, SOX10, and CD34 were consistently negative. *NTRK* rearrangement with various partners was identified in all tumors correlating with tropomyosin receptor kinase(Trk) pan-Trk expression in all tumors and TrkA in three of them. The origin of these tumors is not clear at this time, but it may be possible that they represent a subset of undifferentiated uterine sarcomas [103].

In summary, we have reviewed the widening spectrum of EST, focusing on the subgroup of HG-ESS. Although the current WHO classification only acknowledges YWHAE-related sarcomas in this group, we believe this will be soon modify as the amount of cytogenetic and molecular available evidence increases. Integration of clinical, morphological, and molecular data is becoming of paramount importance in the study of mesenchymal tumors of the uterus.

Author contributions Joana Ferreira, Ana Félix, and Esther Oliva conceived and designed the study, wrote, edited, and reviewed the manuscript. Jochen K. Lennerz researched and analyzed data and edited and reviewed the manuscript. All authors gave final approval for publication. Joana Ferreira takes full responsibility for the work, including the study design, access to data, and the decision to submit and publish the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Norris HJ, Taylor HB (1966) Mesenchymal tumors of the uterus. I. A clinical and pathological study of 53 endometrial stromal tumors. Cancer 19(6):755–766
2. Evans HL (1982) Endometrial stromal sarcoma and poorly differentiated endometrial sarcoma. Cancer 50(10):2170–2182
3. Kempson RL, Hendrickson MR (1988) Pure mesenchymal neoplasms of the uterine corpus: selected problems. Semin Diagn Pathol 5(2):72–98
4. Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR (1990) Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. Am J Surg Pathol 14(5):415–438
5. Tavassoli F.A. DP (ed) (2003) World Health Organization classification of tumours. Pathology and genetics of tumours of the breast and female genital organs. IARC Press, Lyon
6. Kurihara S, Oda Y, Ohishi Y, Iwasa A, Takahira T, Kaneki E, Kobayashi H, Wake N, Tsuneyoshi M (2008) Endometrial stromal sarcomas and related high-grade sarcomas: immunohistochemical and molecular genetic study of 31 cases. Am J Surg Pathol 32(8): 1228–1238
7. Lee C-H, Ou W-B, Marino-Enriquez A, Zhu M, Mayeda M, Wang Y, Guo X, Brunner AL, Amant F, French CA, West RB, McAlpine JN, Gilks CB, Yaffe MB, Prentice LM, McPherson A, Jones SJM, Marra MA, Shah SP, van de Rijn M, Huntsman DG, Dal Cin P, Debiec-Rychter M, Nucci MR, Fletcher JA (2012) 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. Proc Natl Acad Sci 109(3):929–934
8. Lee C-H, Mariño-Enriquez A, Ou W, Zhu M, Ali RH, Chiang S, Amant F, Gilks CB, van de Rijn M, Oliva E, Debiec-Rychter M, Dal Cin P, Fletcher JA, Nucci MR (2012) The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: a histologically high-grade and clinically aggressive tumor. Am J Surg Pathol 36(5):641–653
9. Kurman RJ, Carcangiu ML, Herrington CS, Young RH (eds) (2014) WHO classification of female reproductive organs, 4th edn. IARC, Lyon
10. Tavassoli FA, Norris HJ (1981) Mesenchymal tumours of the uterus. VII. A clinicopathological study of 60 endometrial stromal nodules. Histopathology 5(1):1–10
11. Dionigi A, Oliva E, Clement PB, Young RH (2002) Endometrial stromal nodules and endometrial stromal tumors with limited infiltration: a clinicopathologic study of 50 cases. Am J Surg Pathol 6(5):567–581

12. Su T-F, Chao T-K, Lee H-S, Perng C-L, Nieh S (2014) Malignant potential of an endometrial stromal tumor with limited infiltration: a case report. Int J Surg Pathol 22(6):559–563
13. Oliva E, Clement PB, Young RH, Scully RE (1998) Mixed endometrial stromal and smooth muscle tumors of the uterus: a clinicopathologic study of 15 cases. Am J Surg Pathol 22(8):997–1005
14. Franquemont DW, Frierson HF, Mills SE (1991) An immunohistochemical study of normal endometrial stroma and endometrial stromal neoplasms. Evidence for smooth muscle differentiation. Am J Surg Pathol 15(9):861–870
15. Khalifa MA, Hansen CH, Moore JL, Rusnock EJ, Lage JM (1996) Endometrial stromal sarcoma with focal smooth muscle differentiation: recurrence after 17 years: a follow-up report with discussion of the nomenclature. Int J Gynecol Pathol 15(2):171–176
16. Lillemoe TJ, Perrone T, Norris HJ, Dehner LP (1991) Myogenous phenotype of epithelial-like areas in endometrial stromal sarcomas. Arch Pathol Lab Med 115(3):215–219
17. Yilmaz A, Rush DS, Soslow RA (2002) Endometrial stromal sarcomas with unusual histologic features: a report of 24 primary and metastatic tumors emphasizing fibroblastic and smooth muscle differentiation. Am J Surg Pathol 26(9):1142–1150
18. Baker PM, Moch H, Oliva E (2005) Unusual morphologic features of endometrial stromal tumors. Am J Surg Pathol 29(10): 1394–1398
19. Fadare O, McCalip B, Mariappan MR, Hileeto D, Parkash V (2005) An endometrial stromal tumor with osteoclast-like giant cells: expanding the morphological spectrum. Ann Diagn Pathol 9(3):160–165
20. Kim YH, Cho H, Kyeom-Kim H, Kim I (1996) Uterine endometrial stromal sarcoma with rhabdoid and smooth muscle differentiation. J Korean Med Sci 11(1):88–93
21. Lloreta J, Prat J (1992) Endometrial stromal nodule with smooth and skeletal muscle components simulating stromal sarcoma. Int J Gynecol Pathol 11(4):293–298
22. McCluggage WG, Cromie AJ, Bryson C, Traub AI (2001) Uterine endometrial stromal sarcoma with smooth muscle and glandular differentiation. J Clin Pathol 54(6):481–483
23. Stewart CJR, Leung YC, Murch A, Peverall J (2014) Evaluation of fluorescence in-situ hybridization in monomorphic endometrial stromal neoplasms and their histological mimics: a review of 49 cases. Histopathology 65(4):473–482
24. Oliva E, Young RH, Clement PB, Scully RE (1999) Myxoid and fibrous endometrial stromal tumors of the uterus: a report of 10 cases. Int J Gynecol Pathol 18(4):310–319
25. Kibar Y, Aydin A, Deniz H, Balat O, Cebesoy B, Al-Nafussi A (2008) A rare case of low-grade endometrial stromal sarcoma with myxoid differentiation and atypical bizarre cells. Eur J Gynaecol Oncol 29(4):397–398
26. Kim H-S, Yoon G, Jung YY, Lee Y-Y, Song SY (2015) Fibromyxoid variant of endometrial stromal sarcoma with atypical bizarre nuclei. Int J Clin Exp Pathol 8(3):3316–3321
27. Schoolmeester JK, Sciallis AP, Greipp PT, Hodge JC, Dal Cin P, Keeney GL, Nucci MR (2015) Analysis of MDM2 amplification in 43 endometrial stromal tumors. Int J Gynecol Pathol 34(6):576–583
28. Clement PB, Scully RE (1976) Uterine tumors resembling ovarian sex-cord tumors. A clinicopathologic analysis of fourteen cases. Am J Clin Pathol 66(3):512–525
29. McCluggage WG, Date A, Bharucha H, Toner PG (1996) Endometrial stromal sarcoma with sex cord-like areas and focal rhabdoid differentiation. Histopathology 29(4):369–374
30. Fukunaga M, Miyazawa Y, Ushigome S (1997) Endometrial low-grade stromal sarcoma with ovarian sex cord-like differentiation: report of two cases with an immunohistochemical and flow cytometric study. Pathol Int 47(6):412–415
31. Richmond A, Rohrer A, Davidson SA, Post MD (2017) Low-grade endometrial stromal sarcoma with extensive sex cord differentiation, heterologous elements, and complex atypical hyperplasia: case report and review of the literature. Gynecol Oncol Rep 19:34–38
32. Fekete PS, Vellios F (1984) The clinical and histologic spectrum of endometrial stromal neoplasms: a report of 41 cases. Int J Gynecol Pathol 3(2):198–212
33. Clement PB, Scully RE (1992) Endometrial stromal sarcomas of the uterus with extensive endometrioid glandular differentiation: a report of three cases that caused problems in differential diagnosis. Int J Gynecol Pathol 11(3):163–173
34. Levine PH, Abou-Nassar S, Mittal K (2001) Extrauterine low-grade endometrial stromal sarcoma with florid endometrioid glandular differentiation. Int J Gynecol Pathol 20(4):395–398
35. McCluggage WG, Ganesan R, Herrington CS (2009) Endometrial stromal sarcomas with extensive endometrioid glandular differentiation: report of a series with emphasis on the potential for misdiagnosis and discussion of the differential diagnosis. Histopathology 54(3):365–373
36. Kim YH, Cho H, Kyeom-Kim H, Kim I (1996) Uterine endometrial sarcoma with rhabdoid and smooth muscle differentiation. J Korean Med Sci 11(1):88–93
37. McCluggage WG, Young RH (2008) Endometrial stromal sarcomas with true papillae and pseudopapillae. Int J Gynecol Pathol 27(4):555–561
38. Tanimoto A, Sasaguri T, Arima N, Hashimoto H, Hamada T, Sasaguri Y (1996) Endometrial stromal sarcoma of the uterus with rhabdoid features. Pathol Int 46(3):231–237
39. Oliva E, Clement PB, Young RH (2002) Epithelioid endometrial and endometrioid stromal tumors: a report of four cases emphasizing their distinction from epithelioid smooth muscle tumors and other oxyphilic uterine and extrauterine tumors. Int J Gynecol Pathol 21(1):48–55
40. Lifschitz-Mercer B, Czernobilsky B, Dgani R, Dallenbach-Hellweg G, Moll R, Franke WW (1987) Immunocytochemical study of an endometrial diffuse clear cell stromal sarcoma and other endometrial stromal sarcomas. Cancer 59(8):1494–1499
41. Oliva E, Young RH, Amin MB, Clement PB (2002) An immunohistochemical analysis of endometrial stromal and smooth muscle tumors of the uterus: a study of 54 cases emphasizing the importance of using a panel because of overlap in immunoreactivity for individual antibodies. Am J Surg Pathol 26(4):403–412
42. Chu PG, Arber DA, Weiss LM, Chang KL (2001) Utility of CD10 in distinguishing between endometrial stromal sarcoma and uterine smooth muscle tumors: an immunohistochemical comparison of 34 cases. Mod Pathol 14(5):465–471
43. Arber DA, Chu P (2000) Paraffin-section detection of CD10 in 505 nonhematopoietic neoplasms. Frequent expression in renal cell carcinoma and endometrial stromal sarcoma Am J Clin Pathol 113(3):374–382
44. McCluggage WG, Sumathi VP, Maxwell P (2001) CD10 is a sensitive and diagnostically useful immunohistochemical marker of normal endometrial stroma and of endometrial stromal neoplasms. Histopathology 39(3):273–278
45. Nucci MR, O'Connell JT, Huettner PC, Cviko A, Sun D, Quade BJ (2001) h-Caldesmon expression effectively distinguishes endometrial stromal tumors from uterine smooth muscle tumors. Am J Surg Pathol 25(4):455–463
46. Roy M, Kumar S, Bhatla N, Ray MD, Kumar L, Jain D, Phulware R, Mathur SR (2017) Androgen receptor expression in endometrial stromal sarcoma. Int J Gynecol Pathol 36(5):420–427
47. Jung C-K, Jung J-H, Lee A, Lee Y-S, Choi Y-J, Yoon S-K, Lee K-Y (2008) Diagnostic use of nuclear β-catenin expression for the assessment of endometrial stromal tumors. Mod Pathol 21(6):756–763

48. Adegboyega PA, Qiu S (2008) Immunohistochemical profiling of cytokeratin expression by endometrial stroma sarcoma. Hum Pathol 39(10):1459–1464
49. Rahimi S, Akaev I, Marani C, Chopra M, Yeoh CC (2018) Immunohistochemical expression of different subtypes of cytokeratins by endometrial stromal sarcoma. Appl Immunohistochem Mol Morphol. AIMM
50. Irving JA, Carinelli S, Prat J (2006) Uterine tumors resembling ovarian sex cord tumors are polyphenotypic neoplasms with true sex cord differentiation. Mod Pathol 19(1):17–24
51. Baker RJ, Hildebrandt RH, Rouse RV, Hendrickson MR, Longacre TA (1999) Inhibin and CD99 (MIC2) expression in uterine stromal neoplasms with sex-cord-like elements. Hum Pathol 30(6):671–679
52. Sumathi VP, Al-Hussaini M, Connolly LE, Fullerton L, McCluggage WG (2004) Endometrial stromal neoplasms are immunoreactive with WT-1 antibody. Int J Gynecol Pathol 23(3): 241–247
53. Busca A, Gulavita P, Parra-Herran C, Islam S (2018) IFITM1 outperforms CD10 in differentiating low-grade endometrial stromal sarcomas from smooth muscle neoplasms of the uterus. Int J Gynecol Pathol 37(4):372–378
54. Lee C-H, Ali RH, Rouzbahman M, Marino-Enriquez A, Zhu M, Guo X, Brunner AL, Chiang S, Leung S, Nelnyk N, Huntsman DG, Blake Gilks C, Nielsen TO, Dal Cin P, van de Rijn M, Oliva E, Fletcher JA, Nucci MR (2012) Cyclin D1 as a diagnostic immunomarker for endometrial stromal sarcoma with YWHAE-FAM22 rearrangement. Am J Surg Pathol 36(10):1562–1570
55. Lee C-H, Liang C, Espinosa I (2010) The utility of discovered on gastrointestinal stromal tumor 1 (DOG1) antibody in surgical pathology-the GIST of it. Adv Anat Pathol 17(3):222–232
56. Cossu-Rocca P, Contini M, Uras MG, Muroni MR, Pili F, Carru C, Bosincu L, Massarelli G, Nogales FF, De Miglio MR (2012) Tyrosine kinase receptor status in endometrial stromal sarcoma. Int J Gynecol Pathol 31(6):570–579
57. Klein WM, Kurman RJ (2003) Lack of expression of c-kit protein (CD117) in mesenchymal tumors of the uterus and ovary. Int J Gynecol Pathol 22(2):181–184
58. Caudell JJ, Deavers MT, Slomovitz BM, Lu KH, Broaddus RR, Gershenson DM, Ramondetta LM (2005) Imatinib mesylate (gleevec)—targeted kinases are expressed in uterine sarcomas. Appl Immunohistochem Mol Morphol 13(2):167–170
59. Nakayama M, Mitsuhashi T, Shimizu Y, Ban S, Ogawa F, Ishihara O, Shimizu M (2006) Immunohistochemical evaluation of KIT expression in sarcomas of the gynecologic region. Int J Gynecol Pathol 25(1):70–76
60. Chiang S, Lee C-H, Stewart CJR, Oliva E, Hoang LN, Ali RH, Hensley ML, Arias-Stella JA, Frosina D, Jungbluth AA, Benayed R, Ladanyi M, Hameed M, Wang L, Kao Y-C, Antonescu CR, Soslow RA (2017) BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology. Mod Pathol 30(9):1251–1261
61. Sreekantaiah C, Li FP, Weidner N, Sandberg AA (1991) An endometrial stromal sarcoma with clonal cytogenetic abnormalities. Cancer Genet Cytogenet 55(2):163–166
62. Dal Cin P, Aly MS, De Wever I, Moerman P, Van Den Berghe H (1992) Endometrial stromal sarcoma t(7;17)(p15-21;q12-21) is a nonrandom chromosome change. Cancer Genet Cytogenet 63(1): 43–46
63. Koontz JI, Soreng AL, Nucci M, Kuo FC, Pauwels P, van Den Berghe H, Dal Cin P, Fletcher JA, Sklar J (2001) Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci U S A 98(11):6348–6353
64. Micci F, Panagopoulos I, Bjerkehagen B, Heim S (2006) Consistent rearrangement of chromosomal band 6p21 with generation of fusion genes JAZF1/PHF1 and EPC1/PHF1 in endometrial stromal sarcoma. Cancer Res 66(1):107–112
65. Micci F, Gorunova L, Gatius S, Matias-Guiu X, Davidson B, Heim S, Panagopoulos I (2014) MEAF6/PHF1 is a recurrent gene fusion in endometrial stromal sarcoma. Cancer Lett 347(1):75–78
66. Panagopoulos I, Micci F, Thorsen J, Gorunova L, Eibak AM, Bjerkehagen B, Davidson B, Heim S (2012) Novel fusion of MYST/Esa1-associated factor 6 and PHF1 in endometrial stromal sarcoma. PLoS One 7(6):3–8
67. Dewaele B, Przybyl J, Quattrone A, Finalet Ferreiro J, Vanspauwen V, Geerdens E, Gianfelici V, Kalender Z, Wozniak A, Moerman P, Sciot R, Croce S, Amant F, Vandenberghe P, Cools J, Debiec-Rychter M (2014) Identification of a novel, recurrent MBTD1-CXorf67 fusion in low-grade endometrial stromal sarcoma. Int J Cancer 134(5):1112–1122
68. Micci F, Brunetti M, Dal Cin P, Nucci MR, Gorunova L, Heim S, Panagopoulos I (2017) Fusion of the genes BRD8 and PHF1 in endometrial stromal sarcoma. Genes Chromosom Cancer 56(12): 841–845
69. Micci F, Walter CU, Teixeira MR, Panagopoulos I, Bjerkehagen B, Sæter G, Heim S (2003) Cytogenetic and molecular genetic analyses of endometrial stromal sarcoma: nonrandom involvement of chromosome arms 6p and 7p and confirmation of JAZF1/JJAZ1 gene fusion in t(7;17). Cancer Genet Cytogenet 144(2):119–124
70. Huang H-Y, Ladanyi M, Soslow R (2004) Molecular detection of JAZF1-JJAZ1 gene fusion in endometrial stromal neoplasms with classic and variant histology: evidence for genetic heterogeneity. Am J Surg Pathol 28(2):224–232
71. Chiang S, Ali R, Melnyk N, McAlpine JN, Huntsman DG, Gilks CB, Lee C-H, Oliva E (2011) Frequency of known gene rearrangements in endometrial stromal tumors. Am J Surg Pathol 35(9):1364–1372
72. Hrzenjak A, Moinfar F, Tavassoli FA, Strohmeier B, Kremser M-L, Zatloukal K, Denk H (2005) JAZF1/JJAZ1 gene fusion in endometrial stromal sarcomas. J Mol Diagn 7(3):388–395
73. Nucci MR, Harburger D, Koontz J, Dal Cin P, Sklar J (2007) Molecular analysis of the JAZF1-JJAZ1 gene fusion by RT-PCR and fluorescence in situ hybridization in endometrial stromal neoplasms. Am J Surg Pathol 31(1):65–70
74. Oliva E, de Leval L, Soslow R, Herens C (2007) High frequency of JAZF1-JJAZ1 gene fusion in endometrial stromal tumors with smooth muscle differentiation by interphase FISH detection. Am J Surg Pathol 31(8):1277–1284
75. Hrzenjak A (2016) JAZF1/SUZ12 gene fusion in endometrial stromal sarcomas. Orphanet J Rare Dis 11:15
76. D'Angelo E, Ali RH, Espinosa I, Lee C-H, Huntsman DG, Gilks B, Prat J (2013) Endometrial stromal sarcomas with sex cord differentiation are associated with PHF1 rearrangement. Am J Surg Pathol 37(4):514–521
77. Isphording A, Ali RH, Irving J, Goytain A, Nelnyk N, Hoang LN, Gilks CB, Huntsman DG, Nielsen TO, Nucci MR, Lee CH (2013) YWHAE-FAM22 endometrial stromal sarcoma: diagnosis by reverse transcription-polymerase chain reaction in formalin-fixed, paraffin-embedded tumor. Hum Pathol 44(5):837–843
78. Li H, Wang J, Mor G, Sklar J (2008) A neoplastic gene fusion mimics trans-splicing of RNAs in normal human cells. Science 321(5894):1357–1361
79. Chiang S, Oliva E (2013) Recent developments in uterine mesenchymal neoplasms. Histopathology 62(1):124–137
80. Micci F, Gorunova L, Agostini A, Johannessen LE, Brunetti M, Davidson B, Heim S, Panagopoulos I (2016) Cytogenetic and molecular profile of endometrial stromal sarcoma. Genes Chromosom Cancer 55(11):834–846
81. Lee C-H, Nucci MR (2015) Endometrial stromal sarcoma—the new genetic paradigm. Histopathology 67(1):1–19

82. Gebre-Medhin S, Nord KH, Möller E, Mandahl N, Magnusson L, Nilsson J, Jo VY, Vult Von Steyern F, Brosjö O, Larsson O, Domanski HA, Sciot R, Debiec-Rychter M, Fletcher CDM, Mertens F (2012) Recurrent rearrangement of the PHF1 gene in ossifying fibromyxoid tumors. Am J Pathol 181(3):1069–1077
83. Antonescu CR, Sung Y-S, Chen C-L, Zhang L, Chen H-W, Singer S, Agaram NP, Sboner A, Fletcher CD (2014) Novel ZC3H7B-BCOR , MEAF6-PHF1 , and EPC1-PHF1 fusions in ossifying fibromyxoid tumors-molecular characterization shows genetic overlap with endometrial stromal sarcoma. Genes Chromosom Cancer 53(2):183–193
84. Graham RP, Weiss SW, Sukov WR, Goldblum JR, Billings SD, Dotlic S, Folpe AL (2013) PHF1 rearrangements in ossifying fibromyxoid tumors of soft parts: a fluorescence in situ hybridization study of 41 cases with emphasis on the malignant variant. Am J Surg Pathol 37(11):1751–1755
85. Endo M, Kohashi K, Yamamoto H, Ishii T, Yoshida T, Matsunobu T, Iwamoto Y, Oda Y (2013) Ossifying fibromyxoid tumor presenting EP400-PHF1 fusion gene. Hum Pathol 44(11):2603–2608
86. Enzinger FM, Weiss SW, Liang CY (1989) Ossifying fibromyxoid tumor of soft parts. A clinicopathological analysis of 59 cases. Am J Surg Pathol 13(10):817–827
87. Schoolmeester JK, Sukov WR, Maleszewski JJ, Bedroske PP, Folpe AL, Hodge JC (2013) JAZF1 rearrangement in a mesenchymal tumor of nonendometrial stromal origin. Am J Surg Pathol 37(6):938–942
88. Kao Y-C, Sung Y-S, Zhang L, Chen C-L, Huang S-C, Antonescu CR (2017) Expanding the molecular signature of ossifying fibromyxoid tumors with two novel gene fusions: CREBBP-BCORL1 and KDM2A-WWTR1. Genes Chromosom Cancer 56(1):42–50
89. Sciallis AP, Bedroske PP, Schoolmeester JK, Sukov WR, Keeney GL, Hodge JC, Bell D a (2014) High-grade endometrial stromal sarcomas: a clinicopathologic study of a group of tumors with heterogenous morphologic and genetic features. Am J Surg Pathol 38(9):1161–1172
90. Aisagbonhi O, Harrison B, Zhao L, Osgood R, Chebib I, Oliva E (2017) YWHAE rearrangement in a purely conventional low-grade endometrial stromal sarcoma that transformed over time to high-grade sarcoma. Int J Gynecol Pathol
91. Attygalle AD, Vroobel K, Wren D, Barton DPJ, Hazell SJ, Cin PD, Koelble K, McCluggage WG (2017) An unusual case of YWHAE-NUTM2A/B endometrial stromal sarcoma with confinement to the endometrium and lack of high-grade morphology. Int J Gynecol Pathol 36(2):165–171
92. Chew I, Oliva E (2010) Endometrial stromal sarcomas: a review of potential prognostic factors. Adv Anat Pathol 17(2):113–121
93. Schilder JM, Hurd WW, Roth LM, Sutton GP (1999) Hormonal treatment of an endometrial stromal nodule followed by local excision. Obstet Gynecol 93:805–807
94. Vilos GA, Harding PG, Sugimoto AK, Ettler HC, Bernier MJ (2001) Hysteroscopic endomyometrial resection of three uterine sarcomas. J Am Assoc Gynecol Laparosc 8:805–807
95. Horng HC, Wen KC, Wang PH, Chen YJ, Yen MS, Ng HT, Chang YH, Chang Y, Chao HT, Chao KC, Chuang CM, Ho CH, Huang CY, Hung ZC, Jiang LY, Lau HY, Li HY, Lin CY, Liu CH, Sun PL, Twu NF, Wu HH, Yu HC, Ju FY, Tsai CP, Chang WH, Hsu YM, Lee NR, Chen CY, Chang TC, Chang WC, Chen CH, Chen RJ, Chow SN, Lien YR, Sheu BC, Torng PL, Yen ML, Lee WL, Wang KC, Chang CL, Chen CP, Chen JR, Chen TC, Huang JP, Huang MC, Wang YL, Chang CC, Liu JY, Su HY, Wang YC, Yu MH, Huang LW, Seow KM, Lai TH, Lee FK, Chen CH, Huang BS, Hsiao SM, Sun HD, Wu WY, Teng SW, Chen KH, Hung JH, Lai HC, Yuan CC, Hsieh CH, Wang CJ, Chang SJ, Hung MJ, Hsu ST, Ke YM, Lu CH, Sun L, Chang WC, Hung YC, Lin WC, Wang PH, Chen TH, Li YT, Wu MH, Huang KF, Fu HC, Chen SN, Chiang AJ, Li JY, Te Lin L, Tsai HW, Tsui KH (2016) Uterine sarcoma. Part II—uterine endometrial stromal sarcoma: the TAG systematic review. Taiwan J Obstet Gynecol 55(4):472–479
96. Seagle BLL, Shilpi A, Buchanan S, Goodman C, Shahabi S (2017) Low-grade and high-grade endometrial stromal sarcoma: a National Cancer Database Study. Gynecol Oncol 146(2):254–262
97. Rothmund R, Hartkopf A, Joachim C, Walter CB, Wallwiener M, Kraemer B, Brucker SY, Staebler A, Taran FA (2014) Clinical characteristics, pathological reevaluation, surgical management and adjuvant therapy of patients with endometrial stromal tumors. Arch Gynecol Obstet 290(6):1195–1200
98. Ryu H, Choi Y, Song I, Yun H, Jo D, Kim S, Lee H (2015) Long-term treatment of residual or recurrent low-grade endometrial stromal sarcoma with aromatase inhibitors: a report of two cases and a review of the literature. Oncol Lett 10(5):3310–3314
99. Reich O, Regauer S (2007) Hormonal therapy of endometrial stromal sarcoma. Curr Opin Oncol 19(4):347–352
100. Hoang LN, Aneja A, Conlon N, Delair DF, Middha S, Benayed R, Hensley ML, Park KJ, Hollmann TJ, Hameed MR, Antonescu CR, Soslow RA, Chiang S (2017) Novel high-grade endometrial stromal sarcoma. 41(1):12–24
101. Lewis N, Soslow RA, Delair DF, Park KJ, Murali R, Hollmann TJ, Davidson B, Micci F, Panagopoulos I, Hoang LN, Arias-Stella JA, Oliva E, Young RH, Hensley ML, Leitao MM, Hameed M, Benayed R, Ladanyi M, Frosina D, Jungbluth AA, Antonescu CR, Chiang S (2018) ZC3H7B-BCOR high-grade endometrial stromal sarcomas: a report of 17 cases of a newly defined entity. Mod Pathol 31(4):674–684
102. Mariño-Enriquez A, Lauria A, Przybyl J, Ng TL, Kowalewska M, Debiec-Rychter M, Ganesan R, Sumathi V, George S, McCluggage WG, Nucci MR, Lee C-H, Fletcher JA (2018) BCOR internal tandem duplication in high-grade uterine sarcomas. Am J Surg Pathol 42(3):335–341
103. Chiang S, Cotzia P, Hyman DM, Drilon A, Tap WD, Zhang L, Hechtman JF, Frosina D, Jungbluth AA, Murali R, Park KJ, Soslow RA, Oliva E, Iafrate AJ, Benayed R, Ladanyi M, Antonescu CR (2018) NTRK fusions define a novel uterine sarcoma subtype with features of fibrosarcoma. Am J Surg Pathol 42(6):791–798
104. Croce S, Hostein I, Ribeiro A, Garbay D, Velasco V, Stoeckle E, Guyon F, Floquet A, Neuville A, Coindre J-M, MacGrogan G, Chibon F (2013) YWHAE rearrangement identified by FISH and RT-PCR in endometrial stromal sarcomas: genetic and pathological correlations. Mod Pathol 26(10):1390–1400
105. Amant F, Tousseyn T, Coenegrachts L, Decloedt J, Moerman P, Debiec-Rychter M (2011) Case report of a poorly differentiated uterine tumour with t(10;17) translocation and neuroectodermal phenotype. Anticancer Res 31(6):2367–2371
106. Kurihara S, Oda Y, Ohishi Y, Kaneki E, Kobayashi H, Wake N, Tsuneyoshi M (2010) Coincident expression of beta-catenin and cyclin D1 in endometrial stromal tumors and related high-grade sarcomas. Mod Pathol 23(2):225–234
107. Shah VI, McCluggage WG (2015) Cyclin D1 does not distinguish YWHAE-NUTM2 high-grade endometrial stromal sarcoma from undifferentiated endometrial carcinoma. Am J Surg Pathol 39(5):722–724
108. Lee C-H, Hoang LN, Yip S, Reyes C, Marino-Enriquez A, Eilers G, Tao D, Chiang S, Fletcher JA, Soslow RA, Nucci MR, Oliva E (2014) Frequent expression of KIT in endometrial stromal sarcoma with YWHAE genetic rearrangement. Mod Pathol 27(5):751–757
109. O'Meara E, Stack D, Lee C-H, Garvin AJ, Morris T, Argani P, Han JS, Karlsson J, Gisselson D, Leuschner I, Gessler M, Graf N, Fletcher JA, O'Sullivan MJ (2012) Characterization of the

chromosomal translocation t(10;17)(q22;p13) in clear cell sarcoma of kidney. J Pathol 227(1):72–80
110. Suzuki S, Tanioka F, Minato H, Ayhan A, Kasami M, Sugimura H (2014) Breakages at YWHAE, FAM22A, and FAM22B loci in uterine angiosarcoma: a case report with immunohistochemical and genetic analysis. Pathol Res Pract 210(2):130–134
111. Garg G, Shah JP, Toy EP, Bryant CS, Kumar S, Morris RT (2010) Stage IA vs. IB endometrial stromal sarcoma: does the new staging system predict survival? Gynecol Oncol 118(1):8–13
112. Hemming ML, Wagner AJ, Nucci MR, Chiang S, Wang L, Hensley ML, George S (2017) YWHAE -rearranged high-grade endometrial stromal sarcoma: two-center case series and response to chemotherapy. Gynecol Oncol 145(3):531–535
113. Panagopoulos I, Thorsen J, Gorunova L, Haugom L, Bjerkehagen B, Davidson B, Heim S, Micci F (2013) Fusion of the ZC3H7B and BCOR genes in endometrial stromal sarcomas carrying an X;22-translocation. Genes Chromosom Cancer 52(7):610–618
114. Parra-Herran C, Schoolmeester JK, Yuan L, Dal Cin P, Fletcher CDM, Quade BJ, Nucci MR (2016) Myxoid leiomyosarcoma of the uterus. Am J Surg Pathol 40(3):285–301
115. Arias-Stella AJ, Lewis N, Benayed R, Oliva E, Young R, Hoang L, Cheng-Han L, Soslow R, Antonescu CR, Ladanyi M, Chiang S, Jungbluth A (2018) Novel PLAG1 gene rearrangement distinguishes uterine myxoid leiomyosarcoma from other uterine myxoid mesenchymal tumors. Mod Pathol (Abstract)
116. Allen AJ, Ali SM, Gowen K, Elvin JA, Pejovic T (2017) A recurrent endometrial stromal sarcoma harbors the novel fusion JAZF1-BCORL1. Gynecol Oncol Rep 20:51–53
117. Kao Y-C, Sung Y-S, Zhang L, Huang S-C, Argani P, Chung CT, Graf NS, Wright DC, Kellie SJ, Agaram NP, Ludwig K, Zin A, Alaggio R, Antonescu CR (2016) Recurrent BCOR internal tandem duplication and YWHAE-NUTM2B fusions in soft tissue undifferentiated round cell sarcoma of infancy. Am J Surg Pathol 40(8):1009–1020
118. Huynh KD, Fischle W, Verdin E, Bardwell VJ (2000) BCoR, A novel corepressor involved in BCL-6 repression. Genes Dev 14(14):1810–1823
119. Gearhart MD, Corcoran CM, Wamstad JA, Bardwell VJ (2006) Polycomb group and SCF ubiquitin ligases are found in a novel BCOR complex that is recruited to BCL6 targets. Mol Cell Biol 26(18):6880–6889
120. Ghetu AF, Corcoran CM, Cerchietti L, Bardwell VJ, Melnick A, Privé GG (2008) Structure of a BCOR corepressor peptide in complex with the BCL6 BTB domain dimer. Mol Cell 29(3): 384–391
121. Junco SE, Wang R, Gaipa JC, Taylor AB, Schirf V, Gearhart MD, Bardwell VJ, Demeler B, Hart PJ, Kim CA (2013) Structure of the polycomb group protein PCGF1 in complex with BCOR reveals basis for binding selectivity of PCGF homologs. Structure 21(4): 665–671
122. Ng D, Thakker N, Corcoran CM, Donnai D, Perveen R, Schneider A, Hadley DW, Tifft C, Zhang L, Wilkie AOM, van der Smagt JJ, Gorlin RJ, Burgess SM, Bardwell VJ, Black GCM, Biesecker LG (2004) Oculofaciocardiodental and Lenz microphthalmia syndromes result from distinct classes of mutations in BCOR. Nat Genet 36(4):411–416
123. Yamamoto Y, Tsuzuki S, Tsuzuki M, Handa K, Inaguma Y, Emi N (2010) BCOR as a novel fusion partner of retinoic acid receptor alpha in a t(X;17)(p11;q12) variant of acute promyelocytic leukemia. Blood 116(20):4274–4283
124. Sturm D, Orr BA, Toprak UH, Hovestadt V, Jones DTW, Capper D, Sill M, Buchhalter I, Northcott PA, Leis I, Ryzhova M, Koelsche C, Pfaff E, Allen SJ, Balasubramanian G, Worst BC, Pajtler KW, Brabetz S, Johann PD, Sahm F, Reimand J, Mackay A, Carvalho DM, Remke M, Phillips JJ, Perry A, Cowdrey C, Drissi R, Fouladi M, Giangaspero F, Łastowska M, Grajkowska W, Scheurlen W, Pietsch T, Hagel C, Gojo J, Lötsch D, Berger W, Slavc I, Haberler C, Jouvet A, Holm S, Hofer S, Prinz M, Keohane C, Fried I, Mawrin C, Scheie D, Mobley BC, Schniederjan MJ, Santi M, Buccoliero AM, Dahiya S, Kramm CM, von Bueren AO, von Hoff K, Rutkowski S, Herold-Mende C, Frühwald MC, Milde T, Hasselblatt M, Wesseling P, Rößler J, Schüller U, Ebinger M, Schittenhelm J, Frank S, Grobholz R, Vajtai I, Hans V, Schneppenheim R, Zitterbart K, Collins VP, Aronica E, Varlet P, Puget S, Dufour C, Grill J, Figarella-Branger D, Wolter M, Schuhmann MU, Shalaby T, Grotzer M, van Meter T, Monoranu C-M, Felsberg J, Reifenberger G, Snuderl M, Forrester LA, Koster J, Versteeg R, Volckmann R, van Sluis P, Wolf S, Mikkelsen T, Gajjar A, Aldape K, Moore AS, Taylor MD, Jones C, Jabado N, Karajannis MA, Eils R, Schlesner M, Lichter P, von Deimling A, Pfister SM, Ellison DW, Korshunov A, Kool M (2016) New brain tumor entities emerge from molecular classification of CNS-PNETs. Cell 164(5):1060–1072
125. Ueno-Yokohata H, Okita H, Nakasato K, Akimoto S, Hata J, Koshinaga T, Fukuzawa M, Kiyokawa N (2015) Consistent in-frame internal tandem duplications of BCOR characterize clear cell sarcoma of the kidney. Nat Genet 47(8):861–863
126. Santiago T, Clay MR, Allen SJ, Orr BA (2017) Recurrent BCOR internal tandem duplication and BCOR or BCL6 expression distinguish primitive myxoid mesenchymal tumor of infancy from congenital infantile fibrosarcoma. Mod Pathol 30(6):884–891
127. Kao Y-C, Sung Y-S, Zhang L, Jungbluth AA, Huang S-C, Argani P, Agaram NP, Zin A, Alaggio R, Antonescu CR (2016) BCOR overexpression is a highly sensitive marker in round cell sarcomas with BCOR genetic abnormalities. Am J Surg Pathol 40(12): 1670–1678
128. Ohta Y, Suzuki T, Omatsu M, Hamatani S, Shiokawa A, Kushima M, Ota H (2010) Transition from low-grade endometrial stromal sarcoma to high-grade endometrial stromal sarcoma. Int J Gynecol Pathol 29(4):374–377
129. Amant F, Woestenborghs H, Vandenbroucke V, Berteloot P, Neven P, Moerman P, Vergote I (2006) Transition of endometrial stromal sarcoma into high-grade sarcoma. Gynecol Oncol 103(3): 1137–1140
130. Malpica A, Deavers MT, Silva E (2006) High-grade sarcoma in endometrial stromal sarcoma: dedifferentiated endometrial stromal sarcoma. Mod Pathol. abstract
131. Flicker K, Smolle E, Haybaeck J, Moinfar F (2015) Genomic characterization of endometrial stromal sarcomas with array comparative genomic hybridization. Exp Mol Pathol 98(3):367–374
132. Gremel G, Liew M, Hamzei F, Hardell E, Selling J, Ghaderi M, Stemme S, Pontén F, Carlson JW (2015) A prognosis based classification of undifferentiated uterine sarcomas: identification of mitotic index, hormone receptors and YWHAE-FAM22 translocation status as predictors of survival. Int J Cancer 136(7):1608–1618
133. Halbwedl I, Ullmann R, Kremser M-L, Man YG, Isadi-Moud N, Lax S, Denk H, Popper HH, Tavassoli FA, Moinfar F (2005) Chromosomal alterations in low-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma as detected by comparative genomic hybridization. Gynecol Oncol 97(2):582–587
134. Gil-Benso R, López-Ginés C, Navarro S, Carda C, Llombart-Bosch A (1999) Endometrial stromal sarcomas: immunohistochemical, electron microscopical and cytogenetic findings in two cases. Virchows Arch 434(4):307–314
135. Prat J, Nomonde Mbatani (2015) Uterine sarcomas. Int J Gynecol Obstet 131:S105–S110
136. Hardell E, Josefson S, Ghaderi M, Skeie-Jensen T, Westbom-Fremer S, Cheek EH, Bell D, Selling J, Schoolmeester JK, Måsbäck A, Davidson B, Carlson JW (2017) Validation of a mitotic index cutoff as a prognostic marker in undifferentiated uterine sarcomas. Am J Surg Pathol 41(9):1231–1237