Review paper

New and emerging entities of uterine mesenchymal tumours in the era of molecular testing

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Uterine mesenchymal tumours represent a group of heterogeneous tumours, the classification of which is evolving, especially in the context of a broader use of molecular testing. Some entities can be diagnosed based on the combination of morphological and immunohistochemical features. In other entities, such as endometrial sarcomas with KAT6B/A::KANSL1 fusion, the correct diagnosis cannot currently be achieved without molecular testing. In this review, we focus on some of the new entities in which molecular testing plays an essential role for diagnosis, including tumours with KAT6B/A::KANSL1 fusion, tumours with MEIS1::NCOA2 fusion, and tumours with fusion involving the KDM2B gene. In addition, uterine tumours with whorling and GREB1:CTNNB1 fusion and endometrial stromal tumours with CTNNB1 mutation will be discussed. Other tumours with recurrent molecular alterations not specific to a single entity (such as tumours with PLAG1 fusion or RAD51B fusion) are also mentioned. In summary, molecular testing is a very important part of the classification of uterine mesenchymal tumours. The growing number of emerging entities helps to correctly classify tumours into clinically significant categories. However, these entities should be viewed with caution until their clinical significance is supported by robust data, and molecular findings should always be correlated with morphological features.

Key words: uterine mesenchymal tumours, molecular testing, KAT6B/A::KANSL1 fusion, MEIS1::NCOA2 fusion, CTNNB1 alterations.

Introduction

Several recent original articles, case reports, and reviews have focused on the issue of molecular findings in uterine mesenchymal tumours, and this dynamic area is rapidly changing [1–4]. In our review, we focus on recently described entities that potentially belong to the category of endometrial stromal tumours or enter the differential diagnosis of these tumours. These include sarcomas with *KAT6B/A::KANSL1* fusion, tumours with *MEIS1::NCOA2* fusion, and tumours with fusion involving the *KDM2B* gene. In addition, uterine tumours with *CTNNB1* alterations are discussed, including tumours with *GREB1:CTNNB1* fusion and whorling, and their relation to endometrial stromal tumours with *CTNNB1* mutation. Moreover, some tumours with recurrent molecular alterations that are not specific to a single entity,

such as tumours with *PLAG1* fusion and tumours with *RAD51B* fusion, are also reviewed. Knowledge about these emerging entities is important, as rapid evolution in the field of molecular testing requires correct implementation of molecular findings in the context of morphology, immunohistochemical profile, and clinical data.

Tumours with KAT6B/A::KANSL1 fusion

KAT6B/A::KANSL1 fusion was originally described in three cases of smooth muscle tumours, two of those classified as leiomyomas and one as leiomyosarcoma (LMS) [5–7]. In 2022, Agaimy *et al*. [8] described 13 cases of tumours with these fusions and suggested that tumours with *KAT6B/A::KANSL1* fusion represent a distinct entity. Morphologically, these tumours are rather heterogeneous with overlapping features between endometrial stromal and smooth muscle differentiation (Figure 1). Most cases show features suggestive of fibrous (fibromyxoid) low-grade endometrial stromal sarcoma (LGESS), but hybrid features between endometrial stromal and smooth muscle differentiation are common. Rarely, features suggestive mostly of smooth muscle differentiation are present. Mitotic activity is variable; it can be high, but most cases have less than 5 mitoses/10 HPF. The tumour cells can be spindled, ovoid, or both, with usually oval and less commonly spindle-shaped nuclei. Most cases have low-grade features, but a minority can display high-grade atypia, and without molecular testing these cannot be differentiated from high-grade endometrial stromal sarcoma (HGESS) or undifferentiated uterine sarcoma (UUS). The immunohistochemical profile of these tumours is non-specific with common co-expression of smooth muscle and endometrial stromal markers, which can be restricted in the spectrum of expressed markers, and the extent of positivity is commonly only focal.

A problematic aspect of these tumours is that despite their usually deceptively bland morphology and sharp demarcation, they can behave aggressively. In total, 47 cases have been described to date, with follow-up data available in 34 patients [8–12]. From these, 12 (36%) had aggressive clinical course and either died of disease or have recurrent or persistent disease, and 22 (64%) had no evidence of disease. Currently there are no defined criteria that would allow for a prediction of aggressive behaviour, but some limited data suggest that certain molecular features, such as additional mutations beyond the *KAT6B/A::KANSL1* fusion, differences in mRNA expression, and differences in methylation profiling and copy number alterations, can be helpful in this setting. Nevertheless, more data are needed.

Tumours with MEIS1::NCOA1/2 fusion

MEIS1::NCOA1/2 fusion was originally described in spindle cell sarcomas of the kidney and intraosse-

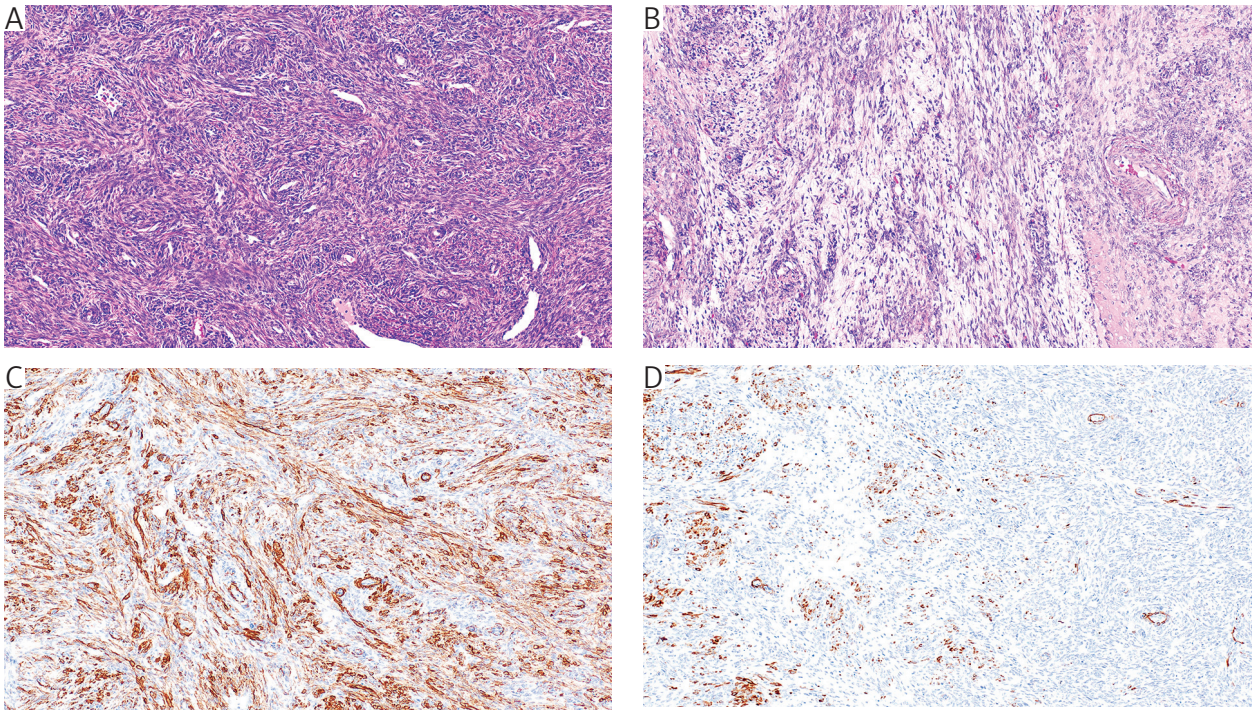

Figure 1. Uterine sarcoma with *KAT6B::KANSL1* fusion. **A**) The tumour shows hybrid features between smooth muscle and endometrial stromal differentiation. **B**) Note the presence of multiple small arterioles and a perivascular whorling pattern. Other areas show spindle-shaped bland cells within a myxoid or hyalinized stroma. **C**) Most tumour cells are positive for smooth muscle actin. **D**) Focal positivity for caldesmon (100×)

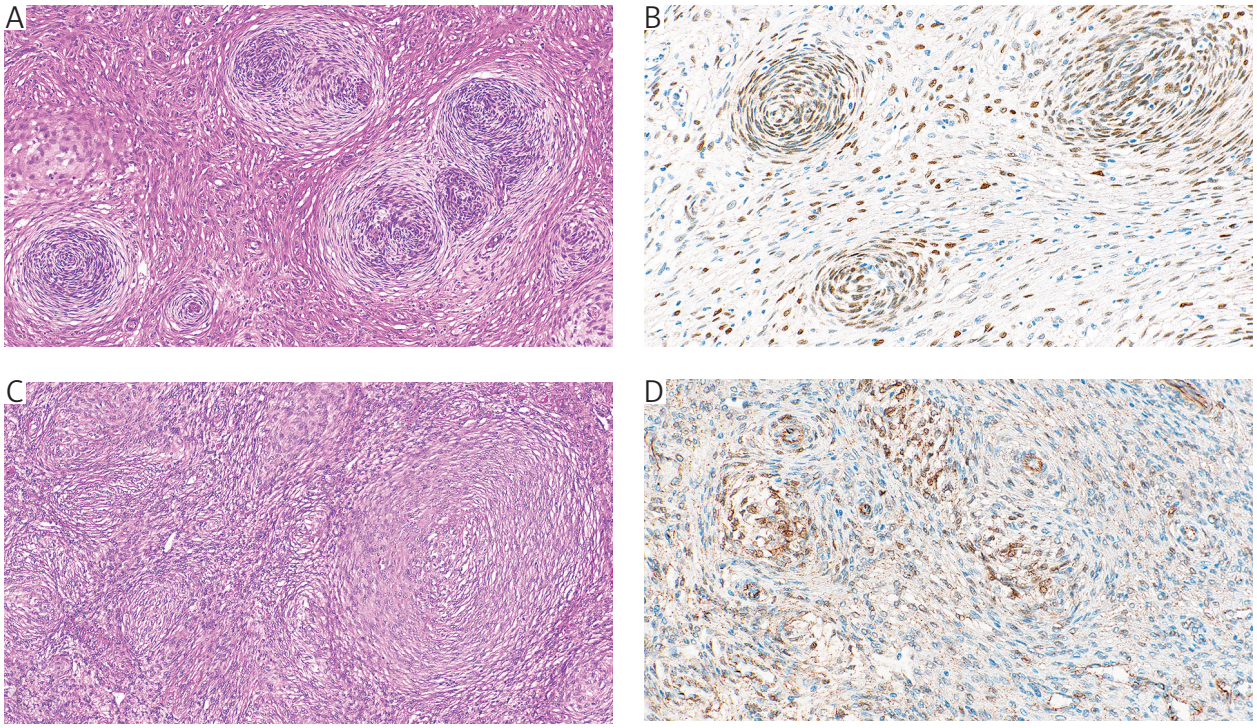

Figure 2. Uterine tumours with *CTNNB1* alterations. **A**) A uterine tumour with *CTNNB1::GREB1* fusion shows a prominent whorling pattern. **B**) Immunohistochemically, most tumour cells show nuclear positivity for β-catenin. **C**) A low-grade endometrial stromal sarcoma with a *CTNNB1* mutation shows a distinct whorling pattern. **D**) Some tumour cells show nuclear positivity for β-catenin (100×)

ous rhabdomyosarcoma [13, 14]. To date, five uterine tumours with these fusions have been described – four with *MEIS1::NCOA2* fusion and one with *MEIS1::NCOA1* fusion [15, 16]. Microscopically, the tumours consist of spindle cells with hyperchromatic coarsely clumped chromatin and variable, but usually high mitotic count (4–40 mitoses/10 HPF). Fascicular, storiform, whorling, and solid patterns were described. Some tumours showed alternating cellularity and areas with myxoid stroma. One tumour had a component of mature adipocytes. Another tumour contained a minor population (30%) of variable cells, including pleomorphic, epithelioid, and cells with cytoplasmic vacuolisation. The immunohistochemical profile of these tumours in nonspecific with variable expression of CD10 and, in most cases, hormone receptors and cyclin D1, with negativity of smooth muscle markers. Concerning biological behaviour, these tumours have a propensity for local recurrence (4/5 patients), and two patients developed lung metastases (one of whom died of disease, while the other shows no evidence of disease 9 months after surgery). In conclusion, of the 5 reported cases one patient died of disease, one is alive with disease (5-month follow-up), and 3 are currently with no evidence of disease (but two of those developed local recurrence and one lung metastasis during the overall course of the disease).

Endometrial stromal tumours with *CTNNB1* alterations

These tumours include endometrial stromal tumours with *CTNNB1::GREB1* fusion and *CTNNB1* mutation (Figure 2). Limited data suggest that these tumours belong to the category of endometrial stromal tumours and can be morphologically characterised by a distinct pattern with peculiar whorling [17]. Nevertheless, some tumours with *CTNNB1* mutation can show features of typical LGESS or its fibroblastic variant.

In total, five cases with *CTNNB1::GREB1* fusion have been described, all characterised by a peculiar pattern with whorling, four of which were sharply demarcated from the surrounding endometrium and were considered as benign [18–20]. *CTNNB1* mutation has been described in one case of endometrial stromal nodule and four LGESS [17, 21, 22]. In a recent study describing three LGESS cases with *CTNNB1* mutation, one showed the described peculiar morphology with whorling and otherwise typical growth pattern of LGESS with angioinvasion and tongue-like invasion [17]. As a result, it has been suggested that tumours with whorling pattern and *CTNNB1* alterations probably represent endometrial stromal tumours, and the same diagnostic criteria for assessment of biological behaviour should be used as for

distinguishing between endometrial stromal nodules and typical LGESS. Nevertheless, neither *CTNNB1* mutation nor *CTNNB1::GREB1* fusion is specific for endometrial stromal tumours, and correlation with morphological features is needed. For example, a single case of a uterine tumour resembling an ovarian sex cord stromal tumour with *CTNNB1:.GREB1* fusion has also been described [23].

Tumours with *KDM2B* fusion

Uterine tumours with *KDM2B* fusion are rare, as only 4 cases have been described in detail to date [24, 25]. In the first reported case, the tumour was microscopically described as consisting of spindle cells with brisk mitotic activity (21/10 HPF) and a moderate amount of myxoid matrix [25]. However, the following study describing three cases found more distinct patterns in all tumours, with alternating hypocellular myxoid or loosely collagenous areas and hypercellular areas consisting of round cells with inconspicuous cytoplasm, moderate cytologic atypia, and mitoses in the range 8–25/10 HPF [24]. Moreover, sex cord-like areas (5–70% of overall tumour) were present. Based on this, the authors suggest that a combination of atypical round cells with myxoid stroma and sex cord-like areas may suggest the possibility of *KDM2B* alteration. The data are however still limited, and more cases are needed to confirm this suggestion. The morphological features of one of our cases are shown in Figures 3A, B (unpublished case; manuscript under preparation). Immunohistochemically, all tumours were characterised by diffuse strong expression of cyclin D1. Other immunohistochemical features were nonspecific, with reported expression of BCOR (single case), focal expression of CD10 (two cases), and progesterone receptor (single case). The examined smooth muscle markers were negative. Clinically, one patient developed widespread disease and died after 29 months, one patient is with no evidence of disease after 9 months of follow-up, another patient is alive after 28 months (however, having refused any treatment, the status concerning possible spread of the disease cannot be assessed), and the last patient was a recent case without available follow-up.

In addition to the above-described cases, two studies focusing on molecular findings in endometrial stromal sarcomas included two tumours with *KDM2B* fusion [26, 27]. One of those had a *KDM2B::CREBBP* fusion and was classified as LGESS, while the other had a *EPC1::KDM2B* fusion and was classified as HGESS. However, no other details about these tumours are available.

Tumours with *RAD51B* fusion

Uterine tumours with *RAD51B* fusion represent a heterogeneous group of lesions with different histogenesis and biological behaviour. *RAD51B* fusion can

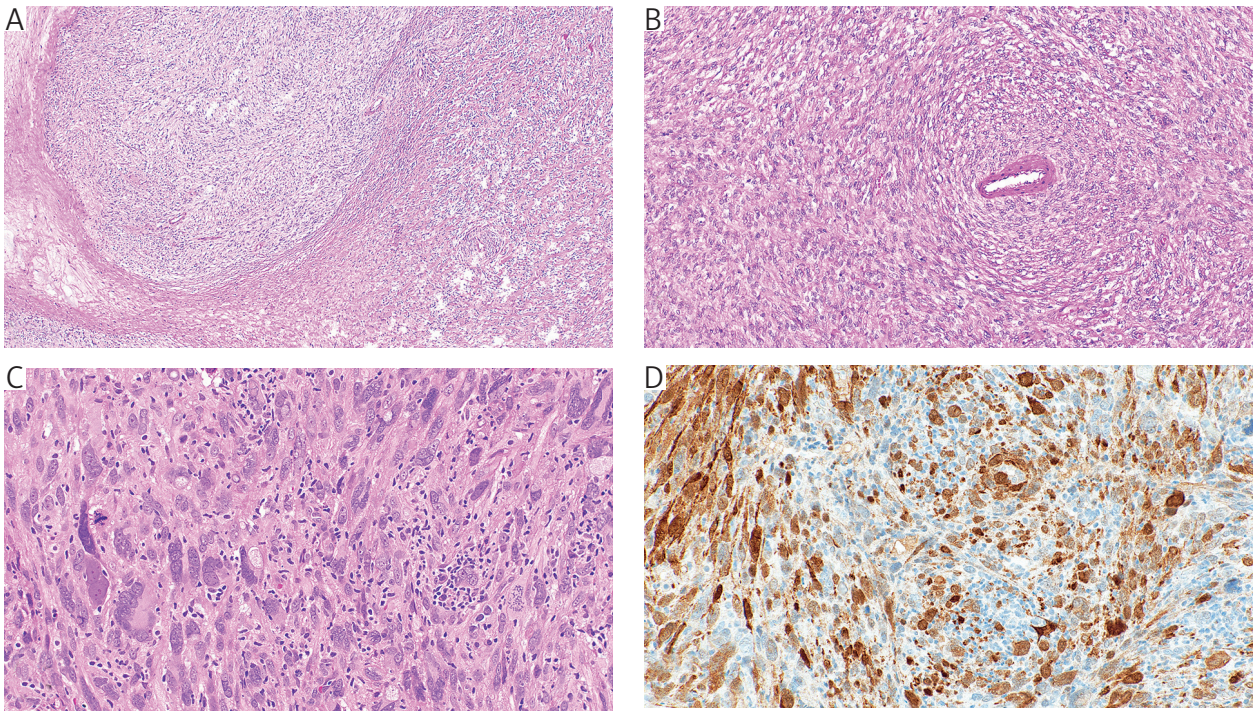

Figure 3. A) Uterine tumour with *KDM2B::EPC2* fusion showing a heterogeneous pattern with variable cellularity, stromal hyalinisation, and oedema (40×). **B**) Areas of increased cellularity composed of monomorphous spindle cells (100×). **C**) Uterine leiomyosarcoma with *RAD51B::VAT1L* fusion composed of pleomorphic cells (200×). **D**) tumour cells show positivity for transgelin (100×)

occur in a subset of benign leiomyomas, the diagnosis of which is based on standard histological criteria [28]. Another entity in which *RAD51B* fusion can occur is uterine PEComa, in which the diagnosis should also be based on morphological and immunohistochemical features [29, 30]. The fusions in PEComa include *RAD51B::RRAGB/OPHN1*, *RAD51B::OPHN1*, and *RAD51B::CEP170* [29–31]. However, PEComas with *RAD51B* fusion seem to be tumours with heterogeneous morphology, including cases consisting of spindle cells, tumours with epithelioid cells, round cells, and pleomorphic cells, commonly with focal sclerosis.

In general, these tumours are characterised by a brisk mitotic activity and propensity for aggressive behaviour, morphologically usually fulfilling the criteria for malignancy [31]. One may speculate whether some of these tumours represent *RAD51B*-fused LMS with aberrant expression of melanocytic markers rather than PEComa, as the expression of melanocytic markers is not specific for PEComa only and (to a certain extent) can also be present in tumours of other histogenesis, including LMS and UUS. To underline this issue, a few cases of tumours classified as LMS with *RADB1B* fusion were described, including cases with *RADB1B::HMGA2* fusion, *RAD51B::PDDC1* fusion, and *PLAG1::RAD51B* fusion [31, 32]. These tumours can consist of spindle cells, epithelioid cells, or can have myxoid features, which are typical also for tumours with *PLAG1* fusion [32]. Morphological features of our LMS case with *RAD51B*::*VAT1L* are presented in Figures 3C, D (unpublished case). Tumours with *PLAG1::RAD51B* fusion seem to be driven by *PLAG1* activation, and in this context *RAD51B* acts as a fusion partner that activates *PLAG1*, rather than a defining feature of a *RAD51B*-altered sarcoma. Undifferentiated uterine sarcoma with *RAD51B* fusion has also been described, including cases with *NUDT3::RAD51B* fusion and *CEP170::RAD51B* fusion [31, 33, 34].

Tumours with *PLAG1* fusion

According to current knowledge, uterine tumours with *PLAG1* fusion are malignant and can be classified as *PLAG1*-rearranged sarcomas because there is no well documented case of *PLAG1* fusion occurring in a benign uterine mesenchymal tumour. Initially, *PLAG1* fusions were described in a subset of uterine myxoid LMS, and it has been estimated that approximately 25% of myxoid LMS harbour this fusion [35]. A subsequent study described 11 cases of uterine tumours with *PLAG1* fusion, including not only 3 cases of myxoid LMS, but also 5 cases of epithelioid LMS, and 3 non-smooth muscle sarcomas with unusual features such as adipocytic differentiation mimicking liposarcoma, osteosarcomatous differentiation, and UUS-like areas [36]. The possible occurrence of unusual differentiation (adipocytic, heterologous) has also been described in other single-case studies [37, 38].

Discussion

A growing number of uterine mesenchymal tumour types are characterised not only by morphology and immunohistochemical features, but also by the presence of recurrent molecular alterations. Due to the increased implementation of molecular testing in research and routine practice, knowledge about the molecular landscape of these tumours is rapidly evolving. Approximately 75% of LGESS harbour recurrent translocations, mostly involving *JAZF1* and *PHF1* genes with variable fusion partners [1, 2]. In HGESS, the only well-defined category are *BCOR*-altered sarcomas, which include sarcomas with *YWHAE::NUTM2A/B* fusion, *ZC3H7B::BCOR* fusion, *BCOR*-ITD, *BCOR* fusion with other partners, and *BCORL1* fusion [39–41]. Nevertheless, HGESS are probably a more heterogeneous category, and the classification of these tumours is currently evolving, with some new emerging entities.

The differential diagnosis of HGESS without a recurrent fusion can be problematic, and tumours of other histogenesis (such as SMARCA4-deficient sarcoma, undifferentiated carcinoma, or PEComa) should be excluded. The distinction of HGESS without a recurrent fusion and UUS can be particularly difficult. In cases of monomorphic tumours with HGESS features but absence of recurrent fusion, tumours of other histogenesis also need to be excluded, including undifferentiated carcinoma, LMS, PEComa, and SMARCA4-deficient sarcoma. Undifferentiated uterine sarcoma is a problematic category, which should include only cases with pleomorphic features, in which molecular and immunohistochemical features of any other distinct entity are excluded. However, molecular alterations should be assessed in all cases in the context of morphological and immunohistochemical findings, and the diagnosis should not be based on molecular results only.

Except for the described emerging entities, increased knowledge about *GLI1*-altered tumours suggests that these tumours represent a distinct entity occurring not only in soft tissues and some visceral organs, but also in the female genital tract [42]. Moreover, there is a growing spectrum of uterine tumours with alternative alterations of tyrosine-kinase receptors, other than tumours with *ALK*, *ROS1,* and *NTRK* alterations, such as tumours with *COL1A1::PDGFRB* fusion, *FGFR1::TACC1* fusion, *RET* rearrangement, *PDGFRB* mutation, *EGFR* mutation, and *ERBB2/3* mutation [43–49].

Typical molecular testing techniques–historically represented by locus-specific fluorescence *in situ* hy-

bridisation and DNA point-mutation analysis – are gradually being replaced by often panel-based nucleic acid testing on either DNA (mutations) or RNA (fusions) or both. Today, these analyses are usually performed using NGS on targeted, cancer-specific panels, which can provide additional layers of information, including detection of large rearrangements, copy-number alterations, tumour mutational burden and microsatellite instability (DNA), or expression profiling (RNA). This expanded readout can be particularly helpful in equivocal cases or in tumours with challenging-to-characterise driver events [2].

Moreover, a growing number of studies now apply advanced classification approaches based on whole-transcriptome RNA-seq or DNA methylation profiling, with promising results not only for sarcoma classification in general but also specifically within uterine mesenchymal tumours [10, 27, 50–52]. Nevertheless, given the rarity of some entities and the frequent biological overlap among tumour types – which is often mirrored by classification outputs – a meaningful description of the uterine sarcoma spectrum remains an active, ongoing effort.

In practice, one should be aware of several important points: some molecular alterations are not specific for a distinct entity and can occur in different tumours; molecular alterations cannot be used for assessment of biological nature of some tumours with certainty; in several entities the defining molecular alterations can differ and often there is a spectrum of alterations rather than a single specific aberration; and recurrent alterations are not necessarily present in all tumours of a particular distinct type. Also, there are some unsolved issues such as the significance of molecular alterations typical for HGESS when present in tumours with features of endometrial stromal nodule [53]. On the contrary, there are some entities, such as tumours with *KAT6B/A::KANSL1* fusion, in which the diagnosis cannot be based on morphological features only, and currently the correct classification of these tumours should be based on this defining molecular alteration.

Concerning practical implementations of molecular findings, one should be aware that tumours with high chromosomal instability, such as UUS and LMS, commonly harbour molecular alterations including fusions, which may represent nonspecific passenger alterations and not driver events characterising the tumours and driving their behaviour. These passenger alterations should not be considered when using molecular finding as an adjunct in differential diagnosis.

Conclusions

Molecular testing has become an important part of classifying uterine mesenchymal tumours. Nevertheless, there are potential pitfalls in the interpretation of molecular findings, which should always be interpreted in the context of morphological and immunohistochemical features. The growing number of emerging entities helps to correctly classify tumours into clinically significant categories; however, these entities should be viewed with caution until their clinical significance is supported by robust data. Molecular characterisation of uterine mesenchymal tumours can be of not only diagnostic, but also of prognostic and predictive significance, enabling targeted treatment in some cases.

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4. Conflicts of interest: None.

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