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Towards a greater understanding of uterine sarcomas

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Uterine sarcomas are rare malignancies. Until relatively recently, they were classified into two categories – leiomyosarcomas and endometrial stromal sarcomas. With increasing refinement of morphological criteria as well as extensive use of immunohistochemistry and molecular testing, there has been an explosive increase in the types and subtypes of uterine sarcomas. More sarcomas have been described since the publication of the 2020 edition of the *Female Genital Tumours* volume of the *WHO Classification of Tumours* [1]. Broadly, uterine sarcomas can be classified as those which have complex genomic alterations and those with simple genomic alterations [2,3].

Leiomyosarcomas, which are the commonest uterine sarcoma, are an example of the former. They typically present as bulky tumours with fleshy, necrotic, and haemorrhagic areas. There are three subtypes: spindled, myxoid, and epithelioid, each exhibiting unique histological features, although mixtures of these subtypes can occur. For the commonest subtype - spindled - diagnosis relies on identifying 2 of 3 criteria:

- marked nuclear atypia
- 10 or more mitoses per 10 high-power fields (each field 0.55 mm in diameter)
- tumour cell necrosis.

Pathologists are also aware of smooth muscle tumours of uncertain malignant potential (STUMP) – a category that is conventionally used in the context of usual/spindle cell smooth muscle tumours. These are rare tumours with morphological features that exceed those of benign leiomyomas but fall short of leiomyosarcoma. There are strict criteria for diagnosis and they need to be distinguished from leiomyomas with bizarre nuclei [1]. Recurrence rates range from 7 % to 28 % [4]. Recurrent tumours may resemble the original STUMP or show features of leiomyosarcoma. The category of STUMP is conventionally used in the context of usual/spindle cell smooth muscle tumours.

Endometrial stromal sarcomas are the commonest uterine sarcomas characterized by simple genomic alterations. Endometrial stromal nodules can be confidently diagnosed from hysterectomy samples and have a benign outcome. Low-grade endometrial stromal sarcomas (LGESS) have an indolent clinical behaviour. The two entities have similar gene fusions, commonest being JAZF1::SUZ12, accounting for half of all cases. There are several other recorded fusions, including JAZF1::PHF1, EPC1::PHF1, and MEAF6::PHF1, while a significant proportion of tumours still lack identifiable fusions [5]. High-grade endometrial stromal sarcomas (HGESS) are divided into three molecular subtypes - YWHAE::NUTM2A/B, BCOR-rearranged, and BCOR internal tandem duplication [1]. There are morphologic and IHC features that vary with the subtype.

Other sarcomas recognised in the uterus include uterine tumours resembling sex cord stromal tumours (UTROSCT), which show gene fusions that have oestrogen receptor 1 (ESR1), growth regulation by oestrogen in breast cancer (GREB1) and nuclear receptor coactivator (NCOA) 1–3 gene family as fusion partners. Of clinical significance is the correlation that has been noted between the fusion partners and the clinical behaviour of UTROSCTs in terms of infiltrative margins, vascular invasion and higher incidence of pelvic recurrence and malignant behaviour [6].

Inflammatory myofibroblastic tumours (IMT) are seen in the uterus as polyps and intramural growths. They have also been described in the placenta. The diagnosis can be suspected by a lymphoplasmacytic infiltrate. ALK fusions are typically seen in 80 % of female genital tract IMTs [7]. Perivascular epithelioid cell tumours (PEComa) are rare uterine mesenchymal tumours showing myomelanocytic differentiation. 90 % of uterine PEComa are sporadic and show genetic alterations in the TSC1 or TSC2 gene. The remainder show germline mutation associated with tuberous sclerosis [8]. Newly described entities include NTRK-rearranged spindle cell tumours, which occur in young women and mostly in the cervix. Targeted therapy against tropomyosine kinase receptors has shown clinical benefit in patients with NTRK-associated sarcomas [9]. Others, including KAT6A/B::KANSL1 fusion tumours, COL1A1::PDGFB fusion uterine sarcoma and MEIS1::NCOA1/2 fusion sarcoma, are being recognised and reported more frequently. SMARC-deficient uterine sarcoma with biallelic inactivation of SMARCA4

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(protein BRG1) or SMARCB1 (protein INI1) of the SWI/SNF complex [10] are tumours with rapid progression and poor outcomes.

This phenomenal increase in knowledge of uterine sarcomas has had an impact on pathological diagnosis, with an increased use of molecular testing, clinical awareness in management and the need for a push towards unified thinking into research on these rare malignancies.

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