Unveiling Endometrial Sarcoma: Insights challenges and Advances

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***Abstract*—The mesenchymal tumor known as endometrial stromal tumor (EST) is a rare and peculiar uterine tumor that has colorful histological, immunohistochemical, and molecular characteristics. ESTs have a morphology that is comparable to that of normal endometrial stromal cells throughout the menstrual cycle's proliferative phase. ESTs were initially categorized as benign or malignant according to the quantity of mitotic cells. Endometrial stromal nodules (ESN), undifferentiated uterine sarcoma (UUS), low-grade endometrial stromal sarcoma (LG-ESS), and high-grade endometrial stromal sarcoma (HG-ESS) are the four categories into which ESTs have lately been categorized by the WHO. When compared to other varieties, HG-ESS has poorer clinical results, making it the most malignant of these categories. Since molecular biology has advanced, Morphological identification has allowed for additional classification of ESTs. Compared to other malignancies, ESTs, including HGESS, are quite uncommon, and so no treatments are being developed for them. Nonetheless, given the tumor microenvironment of typical stromal malignancies, the development of immunotherapy has shown promising results, as documented in numerous distinct stromal tumors and unidentified uterine malignancies. These studies demonstrate the high likelihood of future immunotherapy effectiveness for HG-ESS patients. In order to connect immunotherapy with HG-ESS, the understanding of tumor microenvironment (TME) is required. The TME of HG-ESS shows the mixture of tumor cells, vessels, immune cells and non-malignant stromal cells. Macrophages, neutrophils, dendritic cells and natural killer cells lose their expected functions, but rather show pro-tumoral functions by the matricellular proteins, extracellular matrix and other complicated environment in TME. In order to overcome the current therapeutic limitations of HG-ESS, immunotherapies should be considered in addition to the current surgical strategies. Checkpoint inhibitors, cytokine-based immunotherapies, immune cell therapies are good candidates to be considered as they show promising results in other stromal cancers and uterine cancers, while less studied because of the rarity of ESTs. The new tactics can be used with the existing therapies as well as in other ESTs, based on the advancement of understanding regarding immune therapy in HG-ESS.**

***Index Terms*—Endometrial stromal nodules (ESN), undifferentiated uterine sarcoma (UUS), low-grade endometrial stromal sarcoma (LG-ESS), and high-grade endometrial stromal sarcoma (HG-ESS), Tumor microenvironment (TME), Tumor-associated macrophages (TAMs), Tumor-associated dendritic cells (TADCs), Myeloid-derived suppressor cells (MDSCs), Endometrial sarcoma: One kind of uterine cancer that usually develops in the myometrium, or muscular layer of the uterus, is uterine sarcoma. The majority of uterine malignancies, also known as endometrial cancers or carcinomas, originate in the endometrium, the lining that lines the uterus. Conversely, sarcomas are far less prevalent. Other uncommon forms of sarcoma also originate in the uterine lining's supporting cells.**

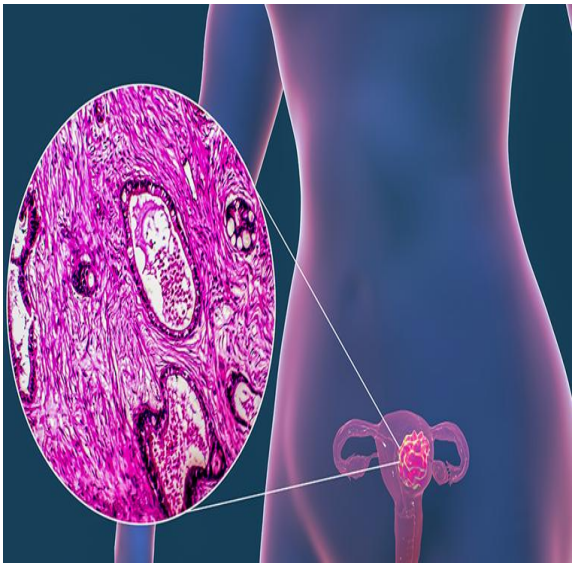

Fig 1: From an article of cancer research centre depicts uterine sarcoma [1]

I. WHO IS SUSCEPTIBLE TO DEVELOPING UTERINE SARCOMA?

Uterine sarcoma may be more likely to occur if you have certain circumstances.

1 Radiation of the pelvis. Your chance of getting uterine sarcoma may increase if you have radiation treatment in the pelvic area. Sarcomas following pelvic radiation are uncommon, but when they do occur, they often manifest five to twenty-five years following radiation.
2 Tamoxifen. Uterine sarcoma risk is increased when tamoxifen is used for breast cancer treatment for a prolonged period of time (five years or longer).
3 Genetics. Having the gene that causes retinoblastoma, an eye cancer, increases your risk of getting some uterine sarcomas.

II. WHAT INDICATIONS AND SYMPTOMS CORRESPOND TO UTERINE SARCOMA?

Uterine sarcoma has many symptoms with non-cancerous growths such fibroids and endometrial carcinoma. If you observe any of these symptoms, it's imperative that you consult your physician:

1. unusual vaginal bleeding that occurs after menopause.
2. Bleeding from the vagina with a foul odor.
3. A growth or bump in your pelvis or vagina.
4. Feeling as though your stomach is full.
5. discomfort in the pelvis.
6. having frequent urination.

Staging of endometrial sarcoma

The following terms can be used by medical professionals when staging endometrial cancer:

Stage 0: The cancerous cells are still visible on the surface of the uterine lining, where they first appeared.[2]

Stage 1: The cancer has progressed from the uterus's inner lining to the endometrium and may have reached the myometrium, which is the uterine wall's middle layer.

Stage 2: The cervix has been affected by the tumor

Stage 3: The tumor has penetrated the uterus and reached adjacent tissue, such as a lymph node or the vagina.

Stage 4: The cancer has progressed to the colon or bladder, and it may have reached other organs such the liver, lungs, or bones.

III. OVERVIEW ON TYPES OF ENDOMETRIAL SARCOMA

According to the World Health Organization's (WHO) guidelines, endometrial stromal nodules (ESNs), low-grade endometrial stromal sarcomas (LG-ESS), high-grade endometrial stromal sarcomas (HG-ESS), and undifferentiated uterine sarcomas (UUS) can be categorized as ESTs.

Low-grade endometrial stromal sarcoma (ESS)

Low-grade endometrial stromal sarcoma (ESS) is a relatively rare type of uterine malignancy characterized by overt endometrial stromal differentiation and mild nuclear features. It typically affects women aged 40–55, although cases in adolescents and children have been reported. Factors like prolonged estrogen exposure, tamoxifen use,[4, 5] or pelvic radiation may be associated with its development.

Symptoms often include abnormal vaginal bleeding, pelvic or abdominal pain, although some women may be asymptomatic. Pelvic examination may reveal an enlarged uterus with irregular contour. Around one-third of cases involve extrauterine spread, often involving the ovaries, making it crucial to distinguish primary ovarian ESS from metastasis from uterine ESS.

Grossly[7], low-grade ESS may appear as irregular intracavity or intramural growths with myometrial permeation. Careful examination is necessary to differentiate it from benign conditions like endometrial stromal nodules.

Microscopically[8], low-grade ESS shows uniform, oval to fusiform cells resembling proliferative endometrial stromal cells. Nuclear atypia is mild, and vascular features may mimic normal endometrial tissue. Myometrial and vascular invasion are key features distinguishing it from benign lesions like endometrial stromal nodules.

Given the challenges in diagnosis, [6] a combination of imaging, hysteroscopy, and possibly local excision may be used for diagnosis and management, particularly in women wishing to preserve their uterus. Detection by cytology is challenging due to the lack of

atypia in the cells, necessitating vigilance from cytopathologists.

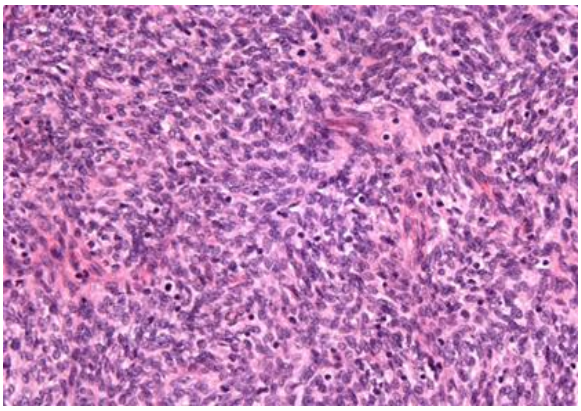

Fig.2 Low-grade ESS. The tumor is composed of generally uniform cells with scant cytoplasm and round to oval nuclei (original magnification × 400, hematoxylin-eosin stain). 3

IV. UNDIFFERENTIATED SARCOMA OF THE OVARIES

Compared to low-grade ESS, undifferentiated endometrial sarcoma is less prevalent. They typically affect postmenopausal women who exhibit uterine hypertrophy and irregular vaginal bleeding. Tumors displaying myometrial invasion, severe nuclear pleomorphism, strong mitotic activity, tumor cell necrosis, or all of these, along with a lack of specific differentiation, are diagnosed with UES. Therefore, UES should be diagnosed only after other high-grade uterine tumors with a sarcomatous component have been ruled out. Grossly, one or more fleshy, tan-yellow to grey intracavity polypoid masses are typically seen when UES is present. Necrosis and bleeding are frequently obvious. Although myometrial invasion is frequent, low-grade ESS is typically not accompanied by the intravascular worm-like plugs.

Histopathologically, UES is not like low-grade ESS; rather, it resembles high-grade leiomyosarcoma or MMMT with a diffuse and destructive infiltrative pattern. The obvious intravascular permeating pattern commonly found in low-grade ESS is typically absent. The neoplastic cells exhibit marked cellular atypia and brisk mitotic activity, almost always exceeding 10 MF/10 HPF. Coagulative tumour necrosis is common and sometimes extensive. Practically, the diagnosis of UES should only be considered after exclusion of a poorly differentiated carcinoma, leiomyosarcoma and MMMT, all of which may be morphologically similar. Extensive sampling and immunohistochemical studies for epithelial and smooth-muscle markers are helpful in the differential diagnosis.

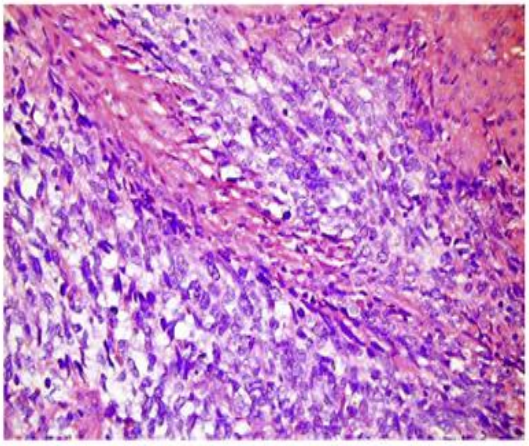

Fig. 3. An undifferentiated endometrial sarcoma showing tumour cells with moderate to marked nuclear pleomorphism. Brisk mitotic activity is noted.

High-grade endometrial stroma sarcoma: the ongoing debate in surgical pathology practice

some low-grade ESS may contain an ‘undifferentiated’ or a high-grade component that retains some endometrial stromal differentiation, indicating that the high-grade component is presumably of endometrial stromal origin.[9,10] The approach of classifying these tumours remains a controversy.[11]-[13] The term ‘high-grade ESS’ is regarded as an alternative term for ‘UES’ to some authorities, whereas others regard it as a separate subtype of ESS. In our opinion, the term ‘high-grade ESS’ is still appropriate for rare high-grade endometrial sarcomas that exhibit endometrial stromal differentiation, particularly when such a tumour seems to have arisen from an associated low-grade ESS. Tumours in this group are composed of uterine sarcomas that have a greater degree of nuclear atypia but maintain a link to endometrial stromal origin either by morphology or growth pattern. The most important feature for distinguishing low-grade ESS from high-grade sarcomas is the resemblance of the neoplastic cells to proliferative endometrial stroma. Some investigators have suggested that such monotonous cytologic uniformity should be viewed as an important feature of endometrial stromal differentiation. A recent study [14]suggests that UES having uniform nuclei, which correspond with high-grade ESS, share some molecular genetics and

immunohistochemical characteristics with that of low-grade ESS and they showed better outcome than UES with nuclear pleomorphism. Moreover, UES featuring uniform nuclei are characterised by frequent simultaneous expression of beta-catenin and cyclin D1. In contrast, UES, with highly pleomorphic nuclei, are all negative for cyclin D1.[15] These findings suggest the UES with uniform nuclei may represent an intermediate subcategory of endometrial stromal tumours and can also be temporarily termed as "high ESS"

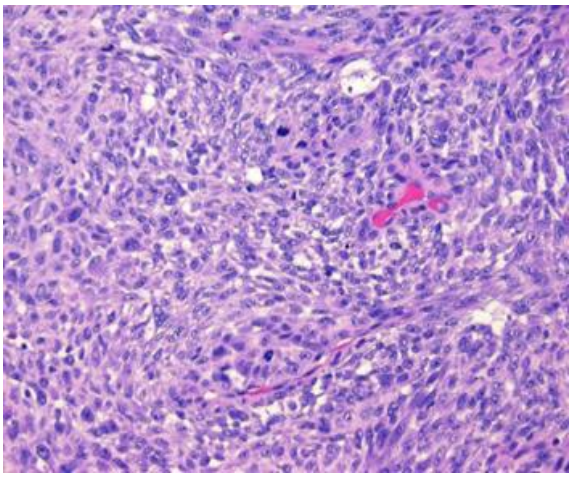

Fig 4: high grade endometrial sarcoma

V. SARCOMA TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) of stromal sarcomas includes various components like non-malignant stromal cells, blood vessels, immune cells, and tumor cells. Matricellular and extracellular matrix (ECM) proteins from stromal cells are crucial for cell movement and signaling. Immune cells in the TME consist of innate (neutrophils, tumor-associated macrophages (TAMs), tumor-associated dendritic cells (TADCs), natural killer (NK) cells) and adaptive (B-cells, T-cells) types. TAMs, TANs, and TADCs typically exhibit pro-tumoral functions, aiding metastasis, invasion, ECM remodeling, and angiogenesis, while suppressing immune surveillance. TAMs resemble M2 macrophages and dominate as sarcomas progress to malignancy due to factors like angiogenic environment and epigenetic changes. TANs mainly consist of pro-tumoral N2 cells. TADCs lose their antigen-presenting function and become pro-tumoral. The composition of these immune cells varies depending on treatment, tumor location, subtype, and genetics. TAMs are a major subset of tumor-associated myeloid cells (TAMCs), along with TANs, myeloid-derived suppressor cells (MDSCs), and Tie2-expressing monocytes (TEMs). T-cell therapies for sarcomas are hindered by immune regulation in the TME, including by mesenchymal stem cells (MSCs), regulatory T cells (Tregs), and TAMs. Targeting TAMs may be crucial for overcoming tumor progression and improving patient survival. Although TAMs phagocytose necrotic tumor cells, they also promote tumor growth and immunosuppression. Increased TAMs in the TME can reduce the effectiveness of CAR T-cell therapy. Further research is needed to understand the role of TAMs in sarcomas and their impact on tumor progression and immune cell profiles.

VI. ENDOMETRIAL CANCERS: IMMUNE SUPPRESSION

A retrospective in silico analysis is called CIBERSORT. Through the deconvolution of gene microarray data sets, CIBERSORT makes it possible to profile immune cells (16, 17). The immunological cell subsets present in tumor tissue were recreated along with their relative amount by deconvolution. By comparing the data of 547 indicators of 22 known peripheral immune cells, the cell type is determined from the gene expression dataset (17). One benefit of this approach is that it can be used to identify immune cell types that are functionally distinct and uncommon, like memory B cells, gd T cells, mast cells, and Tregs (16). This cutting-edge technique has been successfully validated by flow cytometry, which is also utilized to determine the makeup of immune cells that have invaded numerous malignant tumors, including breast and colon cancer (18, 19). Unlike ovarian and other solid tumors, the immune component of endometrial TME has received less research attention. Moreover, significantly less research has been done on ESS than on endometrial adenocarcinomas. Knowing the TME of adenocarcinomas is beneficial in this regard for ESSs. Since TAMs and antitumor adaptive immune responses are particularly prevalent in the stroma of adenocarcinomas, the presence of FoxP3+ Tregs in endometrial malignancies is not the sole problem associated with these tumors. [20]

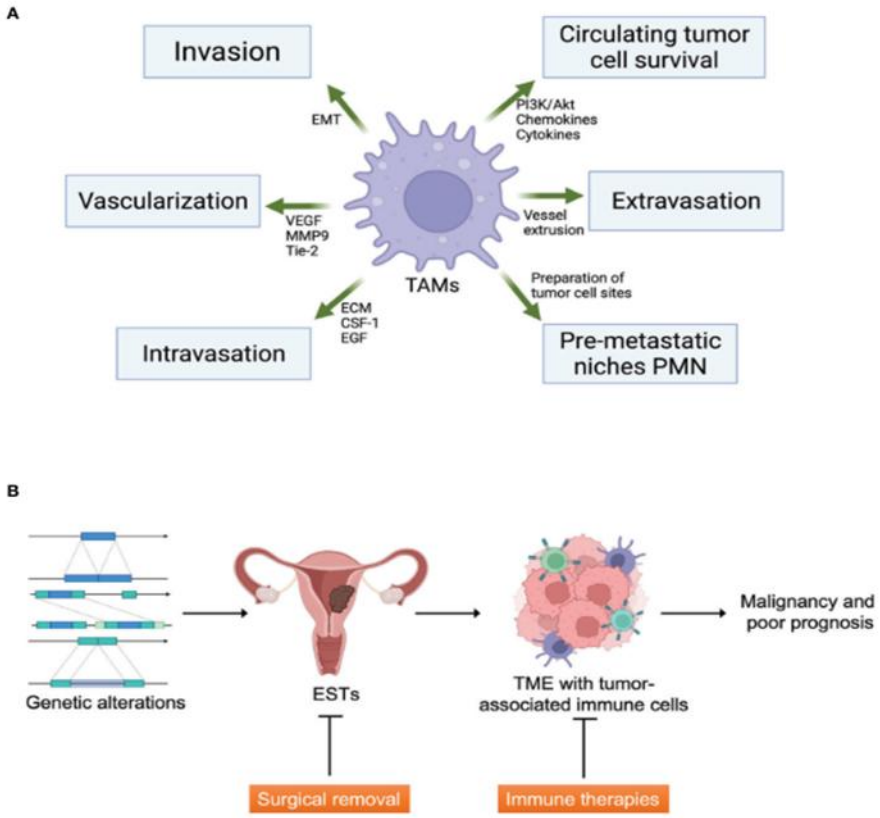

Figure 5 | Tumor microenvironment and ESTs. (A) The functions of tumor-associated macrophages (TAMs) in tumor microenvironment formation. TAMs affect tumor cell metastasis including invasion, vascularization, intravasation, formation of pre-metastatic niches and protection of circulating tumor cells. EMT, epithelial mesenchymal transition; VEGF, vascular endothelial growth factor; MMP9, matrix metallopeptidase-9; ECM, extracellular matrix; CSF-1, colony-stimulating factor-1; EGF, epithelial growthfactor. Created with Biorender.com. (B) The graphical abstract of ESTs and therapeutic strategies. Immune therapies can be an additive strategy to cure malignant ESTs targeting TME. Created with Biorender.com.

VII. ALTERNATIVE IMMUNOTHERAPEUTIC APPROACHES COULD INCLUDE:

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The potential role of the immune system in fighting cancer was observed as far back as 1866, when Wilhelm Busch noted tumor regression in a sarcoma patient who developed an erysipelas infection.21 Immunotherapy for sarcoma traces its roots to at least 1891 when William Coley experimented with what became known as "Coley's Toxin," derived from streptococcal bacteria, to treat osteosarcomas.22, 23 Modern immunotherapy, as described by Paul Ehrlich, aims for a "magic bullet" approach, targeting diseased cells specifically24, 25. The immune system's importance in cancer development is evident from the higher incidence of lymphoid malignancies in immunocompromised individuals and the increased risk of sarcoma in non-immunocompromised patients.26

Immune checkpoint inhibitors, like those targeting PD1 and CTLA-4, have shown promise in cancer treatment by boosting T cell activity. PD1 and its ligand PD-L1 play a significant role in immune evasion by tumor cells. TIM3 and galectin-9, another checkpoint pathway, are under investigation for their potential in cancer immunotherapy. 27(51)

Cytokine-based therapies, such as interferons, stimulate immune responses against cancer cells. Immune cell therapies, including CAR T-cells, genetically engineer T cells to target specific tumor antigens. Recent research suggests neutrophils may

also play a role in activating T cells against tumors. 28 (58)

While these immunotherapy strategies are not extensively studied for HG-ESS currently, their success in other cancers suggests their potential. Given the limitations of current treatments for advanced HG-ESS, such as surgery, radiotherapy, and chemotherapy, the development of immunotherapy offers hope for improved outcomes.

VIII. CONCLUSION

Recent advancements in Next Generation Sequencing (NGS) have significantly enhanced the integration of immunohistochemical and morphological EST classifications, leading to clearer identification of HG-ESS through molecular subclassifications. This molecular approach is pivotal for developing targeted therapies tailored to each subcategory, crucial for devising effective treatment plans for metastatic disease. Consequently, there's a shift towards molecular classification based on genetic analysis, gradually replacing traditional histopathological methods.

Scientific and medical evidence strongly supports the notion that host immunity can be suppressed through various mechanisms to combat stromal cancers. While rare cancers with diverse genetic mutations pose challenges, recent findings elucidate the actions, types, and prognostic significance of Tumor-Infiltrating Lymphocytes (TILs), offering insights into potential therapeutic avenues. TILs can be utilized alone or in conjunction with other molecular therapeutic approaches to enhance tumor cell death, though careful consideration of toxicity is imperative. Although immunotherapies are still in early stages of experimentation and development, their vast potential in cancer therapy necessitates robust exploration, particularly for treating patients with HG-ESS in advanced stages. Traditional therapeutic options like adjuvant radiotherapy and chemotherapy exhibit inconsistent and controversial efficacy. Personalized immunotherapies such as cytokine therapies, immune checkpoint inhibitors, and immune cell therapies have shown remarkable success in treating various advanced cancers, including stromal and uterine cancers. Thus, incorporating immune therapy into the treatment paradigm for HG-ESS patients is warranted. Furthermore, as our understanding of immune therapies in HG-ESS expands, these novel strategies can potentially be extrapolated to encompass en bloc resection-available HG-ESS, LG-ESS, and UUS cases in the future.

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