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Research Article

High-Grade Endometrial Mesenchymal Sarcoma: Current Status and Future Trends

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Abstract

Endometrial Stromal Sarcoma (ESS) is a rare gynecological malignancy originating from endometrial stromal tissue. Representing only a tenth of uterine malignant tumors, ESS is categorized into Low-Grade (LGESS) and High-Grade (HGESS) based on nuclear division. Interestingly, prognostic studies have found no strong correlation between ESS prognosis and nuclear division activity. Undifferentiated Uterine Sarcoma (UUS) represents a spectrum of tumors with varied morphological, clinical, and prognostic features, and lacks a standardized naming convention. In 2014, the World Health Organization grouped ESS into LGESS, HGESS, and UUS based on clinical and pathological attributes. HGESS, despite its rarity, is notorious for its poor prognosis and low survival rate. Its early detection is complicated due to its asymptomatic presentation and ambiguous pathogenesis, leading to debates over treatment approaches. This article delves into the recent research developments concerning HGESS.

More Information

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Molecular biology characteristics

Currently, there is no standardized classification and naming system for UUS. Some researchers have classified UUS into two morphological types: nuclear-consistent UUS and nuclear-polymorphic UUS, which exhibit different immunohistochemical characteristics. Recent developments in clinical biotechnology have revealed that certain UUS cases present a single chromosomal translocation, leading to the fusion of the YWHAE gene with the NUTM2A/2B gene and subsequent development into HGESS. This cell transformation is closely associated with concurrent factors and can be detected through Fluorescence in Situ Hybridization (FISH) and Reverse Transcription-Polymerase Chain Reaction (RT-PCR), which aids in resolving challenges related to morphological diagnosis. Notably, chromosomal translocation is also observed in renal clear cell carcinoma [1].

Clinical characteristics

HGESS is a rare gynecological disease predominantly affecting women aged 45 - 65. Clinical manifestations typically involve abnormal uterine bleeding and the presence of pelvic masses. Due to its low incidence, early-stage HGESS often lacks specific manifestations and tumor markers, making preoperative diagnosis challenging and leading to misdiagnosis as uterine leiomyoma. Although HGESS tends to be detected at a later stage and exhibits a significant malignant tendency, the majority of lesions remain predominantly internal to the uterus. A small proportion of LGESS cases progress to HGESS following multiple recurrences, with the transformation mechanism still not fully understood and potentially associated with tumor clone selection and the tumor microenvironment theory [2].

Pathological diagnosis

Macroscopically, HGESS presents as multiple uterine fibroids within the uterine cavity, accompanied by invasion of the uterine wall. The cut surface typically exhibits a fleshy appearance, with localized bleeding and partial necrosis. Microscopic examination reveals severe infiltration of tumor cells within the muscle layer, displaying a nest-like distribution. The tumor mainly comprises mildly differentiated endometrial stromal cells, occasionally accompanied by spindle-shaped cells. The nuclei of HGESS round cells are relatively larger than those of LGESS, featuring irregular contours and the absence of obvious nucleoli. Although HGESS exhibits higher nuclear division activity, distinguishing it from LGESS based on nuclear division is not feasible. HGESS frequently displays tumor cell necrosis and invasion of vascular gaps [3].

Immunohistochemical analysis demonstrates that round cells in HGESS exhibit strong nuclear expression of cyclin D1, while acute lymphoblastic leukemia/lymphoma antigen, estrogen receptor, and progesterone receptor are negative or

weakly positive in localized areas. In contrast, spindle-shaped cells in HGESS strongly express acute lymphoblastic leukemia/lymphoma antigen, estrogen receptor, and progesterone receptor, similar to LGESS. Furthermore, the cKit gene is positively expressed in the cytoplasm and cell membrane of round cells in HGESS. Interferon-induced transmembrane protein 1, serving as a highly specific marker for endometrial stromal cells, holds significant diagnostic value for HGESS. Notably, the YWHAE-FAM22 fusion is exclusive to HGESS and absent in other tumors, thus aiding in establishing a definitive diagnosis [4].

Treatment and prognosis

Given the highly metastatic and invasive nature of HGESS, targeted treatment is essential. Currently, targeted therapies are commonly employed to treat HGESS patients, effectively reducing the recurrence rate but yielding limited improvement in survival, as the latter is closely associated with tumor metastasis. Adjuvant chemotherapy has limitations but plays an indispensable role due to the propensity of HGESS for distant metastasis. Common chemotherapy regimens include paclitaxel, dacarbazine, and ifosfamide. Combination treatments involve doxorubicin in conjunction with ifosfamide or gemcitabine in combination with dacarbazine, with gemcitabine and docetaxel being widely used in clinical practice [5-7]. The sensitivity of HGESS to hormone therapy remains inconclusive. Some researchers advocate for postoperative adjuvant endocrine therapy as part of comprehensive treatment for HGESS cases exhibiting estrogen and progesterone positivity. Interventions may include megestrol acetate, letrozole, and exemestane, but treatment duration requires further confirmation. Postoperative treatment strategies involve moderate chemotherapy for stage I HGESS patients, chemotherapy and radiation therapy for stage II-III patients and chemotherapy or palliative radiotherapy for others.

In addition to the above treatments, Gemcitabine and docetaxel-Doce gem are also commonly used in the treatment of Leiomyosarcoma (LMS). These two drugs have been shown to be effective in clinical practice, but further studies are needed to determine their effectiveness in the treatment of HGESS [8,9].

Although targeted therapy (referred to as "magic bullets") for HGESS has yet to yield definitive results, it has attracted significant attention due to its promising treatment prospects and substantial research value. Researchers have begun investigating potential targets for HGESS, such as platelet-derived growth factor receptor [10], epidermal growth factor receptor [11], and stem cell growth factor receptor [12]. However, these findings necessitate additional pathological data to serve as clinical evidence and require further confirmation. Pazopanib, a novel anti-angiogenic drug, has demonstrated effectiveness in interfering with tumor growth and survival, particularly in the treatment of uterine sarcoma [13,14]. Cabozantinib, a multitarget small-molecule tyrosine kinase inhibitor, effectively suppresses the activity of relevant targets such as RET and ROS1, which are implicated in tumor angiogenesis and cellular proliferation [15,16]. Currently, international scholars are evaluating the role of cabozantinib in the maintenance treatment of HGESS and UUS, with safety and efficacy being clarified through comparison with placebo [17].

HGESS typically exhibits malignant growth, propensity for distant metastasis, and deep invasion, resulting in prognosis falling between that of LGESS and UUS [18,19]. Compared to LGESS, HGESS demonstrates a greater tendency for disease recurrence, with earlier recurrence leading to a significant decrease in patient survival rate [20]. Currently, the key factors influencing the prognosis of HGESS remain unidentified.

Recent advances in HGESS treatment

With the deepening of scientific research and technological advancement, the treatment strategies for HGESS are constantly evolving. The following are some key advances made in the field of HGESS treatment in recent years: (1). Targeted therapy has become a new direction for HGESS treatment, especially for specific molecular markers and pathways. For instance, Pazopanib, a novel anti-angiogenic drug, has shown potential effects in the treatment of uterine sarcoma [21,22]. (2). Combined treatment strategies, such as the combination of doxorubicin with ifosfamide or gemcitabine with dacarbazine, have been applied in clinical practice, showing potential in improving patient survival rates [23,24]. (3). Although the sensitivity of hormone therapy to HGESS remains uncertain, some researchers suggest adjuvant endocrine therapy for HGESS patients who present positive for estrogen and progesterone [25,26]. (4). Drugs like Gemcitabine and docetaxel-Doce gem have been widely used in leiomyosarcoma (LMS), but their application in HGESS still requires further research.To better understand and evaluate these new treatment strategies, more randomized controlled trials and long-term follow-up studies are needed [27,28].

Discussion

HGESS is an extremely rare malignant tumor of the female reproductive system that lacks overt clinical manifestations, posing challenges for timely detection. It exhibits a predilection for distant metastasis and recurrence [29]. Conventional treatment involves surgical resection, typically employing total hysterectomy combined with bilateral adnexectomy for early-stage patients. The role of lymph node dissection in improving the prognosis of HGESS patients remains uncertain. Moderate radiotherapy effectively reduces the recurrence rate but does not significantly impact survival outcomes [30]. Due to the limited number of HGESS cases and the absence of large-scale support, further research and confirmation are required regarding the molecular signaling presentation, pathological mechanisms, and treatment modalities of HGESS.

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