Uterine leiomyomas (ULs), also known as fibroids, are the most common benign neoplasms of the female genital tract. Approximately 70% of adult women above 50 years of age have ULs, suggesting that this disease usually affects women in their fifth decade of life (1). ULs can be characterized as discrete, round, firm, and often multiple uterine mesenchymal tumors composed of smooth muscle and connective tissue. ULs, including their subtypes, are the most common uterine tumor, with the subtypes accounting for approximately 10% of all UL cases (1). These tumors are most prevalent among African–American women around the world (1). Intravenous leiomyomatosis (IVL) is described as the intravascular proliferation of benign smooth muscle cells and may also be associated with an intrapelvic or extra pelvic extension. IVL progression is more commonly observed in the uterus and rarely infiltrates and proliferates in the broad ligament of the uterus, pelvic veins, and vena cava (2). Patients with IVL have symptoms similar to those of patients with ULs. Although less common, IVLs can be accompanied by chest pain, dyspnea, syncope, or pulmonary embolism due to the involvement of the right heart or pulmonary arteries. Pelvic magnetic resonance imaging (MRI) may help detect early-stage disease. In contrast, computed tomography (CT)-angiography and contrast-enhanced CT can be useful in cases where extrapelvic vasculature extension is present (2).

In patients with IVL, extraperitoneal extension occurs in approximately 30% of patients, involving the pelvic veins, the inferior vena cava, and rarely the heart or pulmonary vessels, which can cause sudden death (3). Studies on IVL etiology have shown that the monochromeity of IVL proliferation is supported by X-chromosome inactivation. Overexpression of the High Mobility Group AT-Hook 2 (HMGA2) gene has been identified in a subset of cases, suggesting a pathogenetic relationship with UL (2,3). Also, studies have reported recurrent 22q and 1p regional losses and 12q gains but no mediator complex subunit 12 (MED12) oncogenic mutations, unlike in UL (2). Histopathological examinations have shown intravascular growth of benign smooth muscle cells, resembling typical UL or its subtypes, in the absence of or outside a UL, and hydropic changes, hyalinization, and the aging phenomenon of myoma cells, with thick-walled vessels, frequently observed. Endometrial stroma and glands have rarely been observed with smooth muscle components (termed intravascular adenomyomatosis). Generally, smooth muscle makers (i.e., aSMA) test positive, whereas clusters of differentiation (i.e., CD10), an epithelial cell marker, tests negative (2,3).

The risk of IVL recurrence is approximately 10%; therefore, a few years later, IVL develops intravascularly. IVL can rarely occur as benign metastatic leiomyoma (BML). BML is found extrauterinely (most commonly in the lungs) and has a clear boundary between the tumor and normal tissue. Often, in patients with a history of UL, BML is a smooth muscle nodular proliferative tumor that appears benign. BML is a hormone-dependent tumor because it expresses estrogen and progesterone receptors.
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IVL is considered to be a female hormone-dependent factor absent in ULs that exhibits a unique behavior of infiltrating blood vessels. Given its positivity for estrogen and PgR, IVL is considered to be a female hormone-dependent tumor (4).

Typically, ULs are benign tumors that do not invade the blood vessels, particularly veins. However, extraterine extension involving pelvic veins, the inferior vena cava, and rarely heart or pulmonary vessels has been observed in approximately 30% of patients with IVL, which can cause sudden death. Therefore, the establishment of IVL treatments is important in clinical practice. In addition, evidence has shown that IVLs express a unique intracellular factor absent in ULs that exhibits a unique behavior of infiltrating blood vessels.

Shi et al. reported that patients with IVL diagnosed incidentally seemed to be at a higher risk of recurrence than those who were diagnosed non-incidentally and underwent complete tumor resection (5). However, incidentally diagnosed patients with IVL can still experience extended disease-free survival after receiving secondary surgical treatment for recurrence (5). The medical evidence obtained from this clinical study provides medical staff with important information for selecting the appropriate treatments for patients with IVL.

Lymphatic metastasis rarely occurs in uterine leiomyosarcoma (uLMS), which is a malignant tumor (frequency, ≤10%), although incidences of hematogenous metastasis have been quite high (6,7). The results of previous studies show the biological similarities between the unique physiological effects of IVL intracellular molecules and the hematogenous metastatic potential of uLMS. A small population of malignant tumor stem-like cells (i.e., malignant tumor stem cells) can migrate to distant organs via intravascular infiltration and form micrometastases. The detailed mechanism by which tumor stem-like cells infiltrate into blood vessels has been unelucidated, and further research is required to understand the initial process of the metastatic mechanism. Based on the results obtained from previous studies, the cluster of differentiation (CD)13, CD44, CD133, etc., which are cell-surface factors, have been reported as markers for cancer stem cells (8). Uterine mesenchymal stem cells (uMSCs) are pluripotent cells found in the stroma of nonhematopoietic bone marrow that also demonstrate self-renewal capabilities. Molecular markers expressed in MSCs include CD44, CD71, CD73 (SH3/4), CD90 (Thy-1), CD105 (SH2), and STRO-1, which are also known as adhesion molecules, CD29, CD106, and CD166 (9,10). A comprehensive examination of these reports suggested that CD44 is appropriate for uMSCs. Therefore, molecular pathological studies were conducted to examine the pathological features of a population of tumor stem-like cells in IVL and uLMS. Similar to uLMS, several mesenchymal tumor stem-like cells (i.e., CD44-positive mesenchymal tumor cells), believed to be able to infiltrate into the vasculature, were found in IVL tissues. This molecular pathological analysis contributes to establishing inhibitors of hematogenous metastasis in IVL, BML, and uLMS.

Similar to malignant tumors, benign tumor tissues comprise a heterogeneous cell population containing many fibroblasts and tumor stem cells other than tumor cells. Hematogenous metastases are present in several patients with uLMS. Even among patients with IVL, an increase in the presence of tumors has been observed in the vein. Particularly, tumor stem cells infiltrate into vessels and promote distant metastases, which are resistant to antitumor agents. Understanding the oncological characteristics of IVL will strongly help establish new diagnostics and targeted antitumor medicines for uterine malignant mesenchymal tumors, such as uLMS.

The proteasome is a multicatalytic proteinase complex and has an ATP-dependent proteolytic activity. The proteasome subunits are involved in antigen processing to generate the major histocompatibility complex (MHC) class I binding peptides. Replacement of proteasome 20S subunit beta 6 (PSMB6) by PSMB9 increases the capacity of the immunoproteasome to cleave model peptides after hydrophobic and basic residues. These immunoproteasome subunits are markedly induced by interferon-gamma (IFN-γ). The function of the immunoproteasome is...
primarily to specifically cleave proteins into shorter peptides, which can then be displayed on the cell surface with the MHC class I. In Psmb9 deficient mice, defective tissue- and substrate-dependent immunoproteasome activity was observed. The expression of the MHC–linked Proteasome 20S subunit beta 9 (PSMB9), which is increased following IFN-treatment, amplifies specific endopeptidase activities of the immunoproteasome. Reports have shown that uterine mesenchymal malignant tumors (i.e., uLMS) spontaneously develop after 6 months of age and above in Psmb9-deficient female mice (11-15). Therefore, clinical studies are being conducted in collaboration with medical institutions to investigate the expression status of PSMB9 in the normal myometrium, UL, uLMS, and other interstitial tumor tissues (16,17). Hematogenous metastases have also been found in Psmb9-deficient female mice (13-15). Based on results obtained from recent clinical research on human clinical materials, uLMS tissues had significantly and explicitly lower PSMB9 expression than UL and normal myometrium tissues.

Based on the significantly reduced PSMB9 expression levels in uLMS, candidate factors as specific biomarkers for uLMS are being investigated using experimental genome-wide methods and histopathological research using human extracted tissues. Previous studies have shown that CD44 or CD133-positive human mesenchymal tumor stem-like cells play an important role in the hematogenous metastasis of uLMS. In previous clinical research, caveolin 1, cyclin B, cyclin E, Ki-67/MIB1, PSMB9, and CD44 have been identified as potential biomarkers for uLMS. Furthermore, the possibility that CD44 is a potential biomarker for IVL has been examined through molecular histopathological experiments with excised uterine tissues (18,19).

Previous clinical studies have revealed the potential mechanisms of tumorigenesis and intravascular infiltration of tumor cells directly mediated by uterine mesenchymal tumor stem-like cells. Efficacy of chemotherapeutic, immunotherapeutic, and target agents against tumor cells, and drug response, are thought to correlate with tumor cell viability by liquid factors released from human uterine mesenchymal tumor stem-like cells. Understanding the characteristics of human uterine mesenchymal tumor stem-like cells contributes to the development of new therapeutic and diagnostic methods for human uterine mesenchymal tumors. Shi et al. reported that patients with IVL diagnosed incidentally seemed to be at higher risk of recurrence than those who were diagnosed non-incidentally and underwent complete tumor resection. Medical evidence obtained thus far will contribute to the development of the optimal treatment for patients with IVL.

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