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Molecular Histopathology of Benign Uterine Mesenchymal Tumors.

Editorial

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Abstract

Uterine leiomyoma is a benign tumor that develops in the myometrium of the uterus. Estrogen is involved in the development and increase of uterine leiomyoma, and even in patients who had strong symptoms before menopause, uterine leiomyoma significantly shrinks after menopause. However, since the cells of uterine leiomyoma have a wide variety of properties, various pathological conditions of uterine leiomyoma are observed in clinical practice. Intravenous leiomyomatosis (IVL) is a relatively rare benign tumor in which smooth muscle tissue grows and spreads intravenously. Intravenous leiomyoma is histologically benign, but it is an important disease that sometimes spreads continuously to the inferior vena cava and the heart and can cause sudden death. Benign metastasizing leiomyoma (BML) is a condition in which metastatic lesions of benign leiomyoma are found in distant organs in women with a history of uterine leiomyoma. In BML, metastasis to the lung is most common. In this editorial, we discuss the several types of uterine leiomyoma with the latest information.

Keywords: Leiomyoma; Intravenous leiomyomatosis; Benign metastasizing leiomyoma; Leiomyosarcoma.

Abbreviations

ER: Estrogen Receptor; CD:Clusters of Differentiation; CT: Computed Tomography; HMGA2: High Mobility Group AT-Hook 2; IVL:Intravenous Leiomyomatosis; MED12: Mediator Complex Sub-unit 12; LMP2: low molecular mass polypeptide 2; MRI: Magnetic resonance Imaging; MSC: Mesenchymal stem cell;PgR:Progesterone Receptor;ULMS:Uterine Leiomyosarcoma.

Uterine leiomyoma, also known as fibroid, is the most common benign neoplasm of the female genital tract. The prevalence of uterine leiomyoma in adult women over the age of 50 is approximately 70%. Therefore, uterine leiomyomas usually affect woman in their fifth decade of life [1]. It is a discrete, round, firm, often multiple uterine tumors composed of smooth muscle and connective tissue. Leiomyoma, including subtypes, is the most common uterine tumor. The subtypes account for approximately 10% of leiomyomas [1]. These tumors are most prevalent among African-American woman and least common among Asian woman. Intravenous leiomyomatosis (IVL) is an intravascular growth of benign smooth muscle cells in the absence of or beyond the confines of a leiomyoma,

sometimes with pelvic or extrapelvic extension. IVL is more commonly seen in the uterus; it rarely involves the broad ligament, pelvic veins, and vena cava [2]. Patients with IVL have symptoms similar to those encountered in patients with leiomyomas. Less commonly, they present with chest pain, dyspnea, syncope, or pulmonary embolism due to right heart or pulmonary artery involvement. Pelvic Magnetic Resonance Imaging (MRI) may help to detect early-stage disease; computed tomography (CT)-angiography and contrast-enhanced CT are useful if there is extension to extrapelvic vasculature [2].

In case of patients with IVL, extrauterine extension occurs in about 30% of patients, involving pelvic veins, the inferior vena cava, and rarely heart or pulmonary vessels, leading to sudden death [3]. The studies regarding pathogenesis of IVL reveal that the monoclonality of IVL proliferation is supported by X chromosome inactivation. Involving *High Mobility Group AT-Hook 2(HMGA2)* gene, and HMGA2 protein overexpression have been identified in a subset of cases, suggesting a pathogenetic relationship with uterine leiomyoma [2,3]. Recurrent 22q and 1p regional losses and 12q gains have also been reported, but no *Mediator Complex Subunit 12(MED12)* mutations, unlike in leiomyoma [2]. Histopathological examinations show that there is intravascular growth of benign smooth muscle cells, resembling typical leiomyoma or its subtypes, in the absence of or outside a leiomyoma; hydropic change, hyalinization, and thick-walled vessels are frequent. Rarely, endometrial stroma and glands may be seen admixed with the smooth muscle component (termed intravascular adenomyomatosis). Smooth muscle makers are generally positive and Clusters of differentiation 10 (CD10) negative [2,3].

Recurrence, the risk of which is about 10%, may occur years later, either within veins or rarely as benign metastasizing leiomyoma (BML). BML leiomyoma is an extrauterine (most commonly in the lung), well-demarcated, often nodular proliferation of benign-appearing smooth muscle, often in patients with a history of uterine leiomyoma(s) [4]. These lesions of BML are considered to represent spread from a histologically benign uterine smooth muscle tumor. The studies regarding pathogenesis demonstrate that benign BML is clonally derived from uterine leiomyoma [4]. Molecular analysis reveals broad similarities with the mutations and expression abnormalities found in uterine leiomyoma, including *MED12* mutations. However, cytogenetic analysis highlighted chromosomal aberrations not typically found in uterine leiomyomas, including 19q and 22q terminal deletion. Histopathological examinations show that there is usually a well-demarcated proliferation of intersecting fascicles of spindle cells with moderate eosinophilic cytoplasm and blunt-ended nuclei; the cells are cytologically bland, with minimal to absent mitosis. BML may be cellular or admixed with adipose tissue [4]. In the lung, it tends to have a peribronchiolar pattern and may entrap alveolar spaces peripherally. Estrogen Receptor (ER) and progesterone receptor (PgR) are positive [4].

Typically, uterine leiomyomas are benign tumors do not invade into the blood vessel containing the vein, however, in case of patients with IVL, extrauterine extension occurs in about 30% of patients, involving pelvic veins, the inferior vena cava, and rarely heart or pulmonary vessels, leading to sudden death. Therefore, in clinical practice the development of treatments for IVL is important.It is thought that a unique intracellular factor is expressed in IVL in order to perform a peculiar behavior of infiltrating into a blood vessel that uterine leiomyoma does not have. Shi *et al*. reported that IVL patients diagnosed incidentally seems to have a higher risk of recurrence when compared with those diagnosed non-incidentally and underwent complete tumor resection. However, incidentally diagnosed IVL patients can still have a long disease-free survival after receiving a secondary surgery treatment after recurrence.

In uterine leiomyosarcoma (uLMS), which is a malignant tumor, lymphatic metastasis is rare (frequency 10% or less), and hematogenous metastasis is observed at high frequency [5,6]. There may be similarities between the physiological actions of the unique intracellular factors of IVL and the hematogenous metastatic potential of uLMS. Small population of stem-like malignant tumor cells (i.e., malignant tumor stem cells) migrate to distant organs via intravascular infiltration, constructing micrometastases. As a result of previous studies, CD13, CD44, CD133, etc. have been reported as markers for cancer stem cells [7]. Mesenchymal stem cells (MSCs) are pluripotent cells found in stroma of non-hematopoietic bone marrow, and have a pluripotency. In addition, MSCs also have self-renewal capabilities. As molecular markers expressed in MSCs, CD105 (SH2), CD73 (SH3/4), CD44, CD90 (Thy-1), CD71 and Stro-1 are known as well as adhesion molecules CD106, CD166 and CD29 [8,9]. Comprehensive examination of these reports suggests that CD44 is appropriate as a marker for uterine mesenchymal tumor stem cells.

Therefore, we examined the pathological features including population of tumor stem-like cells in Intravenous leiomyomatosis and uLMS by molecular pathological studies. As a result, the molecular pathological features common to the IVL and uLMS was observed. Similar to uLMS, many mesenchymal tumor stem-like cells i.e., CD44-positive mesenchymal tumor cells, believed to have the ability to infiltrate into the vasculature were found in the tissue of the IVL. The results obtained from this molecular pathological analysis contribute to the development of inhibitors of hematogenous metastasis in IVL, BML, and uLMS.

Like the malignant tumor, the nature of the benign tumors is different for each patient. That is, a benign tumor tissue is a heterogeneous cell population containing a large amount of fibroblasts and tumor stem cells other than tumor cells. Hematogenous metastases are present in many patients with uLMS. Even IVL, tumor increased in the vein is observed. In particular, tumor stem cells infiltrate into vessels and undergo distant metastasis, and have resistance to antitumor agents. Understanding the oncological properties of IVL contributes to the development of new targeted antitumor agents for malignant mesenchymal tumors such as uLMS.

The proteasome is a proteolytic enzyme complex consisting of multiple subunits that degrades ubiquitinated proteins in eukaryotic cells and plays a central role in proteolytic degradation. Stimulation of interferon-gamma (IFN-β) induces the expression of beta subunits and constitutes the immunoproteasome, which regulates gene expression and cell proliferation by controlling the degradation of intracellular proteins. The expression of the major histocompatibility complex–linked low molecular mass polypeptide 2/β1i (LMP2/β1i) subunit, which is increased by treatment with IFN-β, amplifies specific endopeptidase activities of the immunoproteasome. Reports demonstrated that uterine mesenchymal malignant tumor, i.e., uLMS spontaneously developed after six months of age in *Lmp2/β1i*-deficient female mice [10-14]. Studies have shown that the prevalence of uLMS in *Lmp2/β1i*-deficient mice is approximately 37% at 12 months of age [12-14]. Therefore, in clinical research by a collaboration of medical institutions, the expression status of LMP2/β1i was examined in 74 cases with normal myometrium, uterine leiomyoma, uLMS and other uterine mesenchymal tumour tissues obtained from the pathological file by immunohistochemical (IHC) staining using an anti-human LMP2/β1i monoclonal antibody [15,16]. Hematogenous metastases were also found in the *Lmp2/β1i*-deficient female mouse [12-14]. The incidence of other malignancies (i.e. hepatocellular carcinoma, etc.) in *Lmp2/β1i*-deficient mice has been reported to be 1% or less [12-14]. As the results from recent clinical research with human clinical materials, the expression level of LMP2/β1i was significantly explicitly reduced in the uLMS tissues compared with those in the uterine leiomyoma and normal myometrium tissues [15-17].

Based on the markedly reduced expression level of LMP2/β1i, candidate factors as biomarkers specifically expressed in uLMS have been sought using genome-wide experimental methods with human-extracted tissues. As a result, CAVEOLIN 1, CYCLIN B, CYCLIN E, Ki-67/MIB1 and LMP2/β1i were identified as biomarker candidate factors expressed explicitly in uLMS. The differential diagnostic method with IHC staining using a combination of several monoclonal antibodies to LMP2/β1i and other candidate cellular factors such as CAVEOLIN 1, CYCLIN B, CYCLIN E, Ki-67/MIB1 and CD44 has been investigated for uterine mesenchymal tumours, including uLMS [18,19].

Our work describes a potential mechanism regarding tumorigenesis and Intravascular infiltration caused by uterine mesenchymal tumor stem-like cells. The effectiveness of chemotherapeutic agents, immunotherapy agents, and targeted agents on tumor cells as well as drug response will be assessed according to tumor cell viability through released biomarkers from human uterine mesenchymal tumor stem-like cells. The characteristics of these human uterine mesenchymal tumor stem-like cells will provide insights into the development of novel therapeutics and diagnostic methods for human uterine mesenchymal tumor.

Conclusions

IVL and BML are rare clinical conditions of benign mesenchymal tumors. Cases of IVL extending from the uterus to the heart have been reported. In addition, cases of benign metastatic leiomyoma with lung metastases have been reported. The diagnosis of a mass extending from the inferior vena cava to the right heart system in middle-aged and older women should be done with caution. In addition, even in the case of uterine leiomyoma, it is necessary to pay attention to the accumulation in distant organs by imaging examination.

Contributors list

TH performed most of the clinical medicine and coordinated the project. TH, and IK conducted the diagnostic pathological studies. ST donated LMP2/b1i deficient mice, and discussed molecular findings and information. TH created the study and wrote the manuscript. NY, and IK and carefully reviewed this manuscript and commented on the aspects of medical science. IK shared information on clinical medicine and oversaw the entirety of the study.

Conflicts of Interest: The authors declare no potential conflicts of interest.

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