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Uterine fibroid: common features of widespread tumor
(Review article)

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Abstract: Leiomyoma is the most frequent benign monoclonal tumor (cells behave identically in culture) of the female reproductive system. It affected almost 50% of childbearing age women, deteriorating the quality of life and may cause infertility. The unique features of this pathology is the absence of detailed understanding of pathogenic mechanisms and continuous morbidity among any age groups. Despite the huge amount of articles and studies related to leiomyoma, review pretend to depict herein actual and non-trivial information. This review assemble a versatile description of medical and biological aspects of leiomyomas. Explanation of genetic, molecular, pathophysiological mechanisms of uterine fibroid growing predetermine marked clinical symptoms of pathology. Mentioned model systems show multivariation of leiomyomas in human and animals. Review gives an opportunity analyze separate facets and collect it in one deep understanding of leiomyomas.

Key words: leyomyoma; uterine fibroid; infertility; endometrium; myometrium; steroid hormones.

Introduction

Uterine fibroids (correctly called leiomyomas or myomas) are monoclonal diploid highly frequent gynecological tumors that arise from the uterine smooth-muscle tissue and are characterized by the production of excessive quantities of extracellular matrix (ECM). Uterine

leiomyomata (UL) affects up to 80% of all women in their reproductive age. These benign tumors can develop into significantly sized lesions (from 10 mm to 20 cm). According to literature data, the youngest patient with LM was 19 years old, the oldest — 71. Majority cases are diagnosed between the ages of 28 and 52 years [1]. Histologically, they are neoplasms composed of disordered myometrium cells buried in abundant quantities of ECM, which formation also accounts for a substantial portion of tumor expression. Uterine fibroids are always benign [2, 3]. According to data from one survey, changes in fibroid size ranged from 89% shrinkage to 138% growth, with a median of 9% change in volume in a 6-month period. Moreover, fibroids can have growth spurts [4, 5].

Historical notes

The uterine leiomyoma has been known for human population since antique. Its first mention referred to Hippocrates as "uterine stones", while Galen, in the second century of the Christian era, described the findings as "scleromas". Moreover, some mummies, which exhibited in the English Museum in London, has calcified pelvic masses located though radiographic techniques which are suggestive of uterine leiomyoma [6].

Matthew Baillie, a Scottish physician and pathologist at St George's Hospital in London, first described uterine leiomyomas in 1793. Rokitansky (1860) and Klob (1863) introduced the "fibroid" term, while Virchow, the famous German Pathologist, demonstrated that those tumors originated from the uterine smooth muscle. Thus, the term "myoma" became current in clinical use [7].

The first laparotomy consequent to myoma indication was performed in 1809, in Danville, USA. On that occasion, the surgeon Ephraim McDowell operated Mrs. Jane Todd Crawford, a cousin of President Abraham Lincoln [6].

Prevalence

Assuredly, UL is the most common tumor among gynecological pathology. Different surveys and publications present own percentages of its prevalence and sometimes its data are contradictory. Despite all, insist on majority of uterine fibroids among gynecological pathology. Tumors occur in 77% of women and has a slight difference between women with different skin color. Nearly 70% of white women and more than 80% of black women will have had at least one fibroid. Some studies prove this difference in a race by Vitamin D deficiency, naturally occurring in women with dark skin. However, this hypothesis is still discussible. In addition, black women have higher level of aromatase and elevated levels of estrogen in tissue. The prevalence of clinically significant fibroids peaks in the perimenopausal years and declines after menopause [8–11]. Interestingly, that growth rates also appear to be related to race. In the Fibroid Growth Study, white women had significantly lower UL growth rates as they approached menopause, whereas African American women's growth rates remained unchanged [4].

The incidence of uterine fibroids in Poland is not precisely defined in fact, epidemiological studies indicate a large variation of the results (from 20% to 40% of women) [12].

Risk factors

Despite the high prevalence of UL, epidemiological studies on their frequency and risk factors are poorly [1].

An early onset of menarche (before the age of 10) mentioned as a risk factor of UL developing, whereas a menarche over the age of 16 seems to decline the same risk [13, 14].

The adipose tissue are one of aromatase's source, where adrenal and ovarian androgens converts into estrogens. In fact, in UL tissue both enzymes, which convert androgens in estrogens (CYP19 aromatase and 17-β-hydroxysteroid dehydrogenase type I) are overexpressed [1, 15]. Obesity is an established risk factor for UL development. It can lead to increased producing of estrogens and decreased synthesis of sex hormone binding globulin [13]. Surveys showed that adiponectin could inhibit leiomyoma growth in culture [16]. Moreover, the risk of UL increased in 21% with each 10 kg increase in body weight and with increasing body mass index [13].

The opposite effect has smoking. Several studies have revealed that nicotine inhibits aromatase. Smoking also impact on the 2-hydroxylation pathway of estradiol metabolism, which can lead to decline bioavailability of estrogen target tissues [13].

During pregnancy, leiomyomas are not inevitably growing. In most studies, the majority of leiomyomas remained the same size. Additionally, spontaneous shrinking was found in nearly 80% of women within 6 months of delivery [4].

Conflicting data coexist about the relationship between oral contraceptives (OC) and the growth of UL. This could be explained by the different content of estrogens and the type of progesterone in each specific OC preparation [13].

Coexistence of leiomyomata and others diseases were observed by many studies. According to published data, suggested that UL would cause hypertension as a consequence of urinary tract obstruction by large tumors. Moreover, inflammation process or infectious diseases can be associated with developing of some neoplasms. For instance, children infected with human immunodeficiency virus have increased incidence of both leiomyoma and leiomyosarcoma in several organ [17]. Hyperinsulinemia is considered as a risk factor since insulin may influence UL development through direct promotion of myometrial smooth muscle cell proliferation or by increasing circulating levels of ovarian hormones [14].

Classification

Lack of a standardized nomenclature and classification makes communication difficult in clinical care and research. Traditionally classification of leiomyomas is based on the type of growth and location within the uterus [1].

There are four primary types of leiomyoma classified primarily by location in the uterus.

— subserous (located just beneath the serosal surface);
— intramural (found primarily within the thick myometrium);
— submucous (located beneath the endometrium);
— pedunculated (fibroids that grow on a small stalk that connects them to the inner or outer wall of the uterus).

The most common is the intramural uterine leiomyoma. Moreover, the tumor can occur in the cervix (approximately 8% of cases) and their growth may proceeds towards the space between the layers of the broad ligament (intralaminar variant of leiomyoma).

Fibroids can be single and multiple. If the uterus contains too many to count, it is referred to as diffuse uterine leiomyomatosis. In each location however multiple tumors are characterized by the presence of intratumoral septa [18].

Also, in clinical practice exist separate and detailed the European Society of Gynecological Endoscopy (ESGE) of submocous leiomyomas. It is can be useful when considering therapeutic options, including the surgical approach. The most widely used system categorizes the leiomyomas into three subtypes according to the proportion of the lesion's diameter that is within the myometrium, usually as determined by saline infusion sonography (SIS) or hysteroscopy. The International Federation of Gynecology and Obstetrics (FIGO) uses the same system of classification of causes of abnormal uterine bleeding, but add some extra categories [19].

Pathogenesis

There are not exist one theory that may explain why UL are so common nowadays. Importantly consider in depth all biochemical pathways, genetic background, risk factors as triggers that leads to transformation normal myometrium in pathological focuses.

ECM of fibroids is not only excessive in amount, but it is abnormally formed, and the components of such critical structural elements, such as the orientation of the fibrils and their length are altered in fibroids. Collagens are loosely packed and arranged in a nonparallel, disorganized manner. There is also greater remodeling of the ECM in UL as they express higher levels of specific metalloproteinases (MMPs) including MMP2 and MMP11 [20]. Myofibroblast cells produce collagen and others components of the ECM, but its inappropriate function to cause fibrosis. Some researchers suggested that the formation of fibrosis is mistaken in normal reparation, which periodically occur in the uterus. Leiomyoma and keloid have similar gene characteristics [8].

It had been proved by time and studies that the risk of leiomyomas uteri inherited. The first-degree relatives of affected women have a 2.5 times increased risk of developing fibroids. Mutations in genes, which encode cellular ferments, might be a reason of fibrotic phenotype of leiomyomas. SLK gene encoding STE20-like kinase, that expressed in proliferating myoblasts and is activated by epithelial disruption. This ferment play role in myogenic differentiation and cell motility. Activated by scratch wounding. A-kinase anchor protein-13 (AKAP13) is associated with cytoskeletal filaments in fibroid cells, which abnormally respond to mechanical stress and as a result – accompanied by abnormal extracellular matrix deposition [13, 21].

Moreover, frequently in patients with leiomyoma exist a series of mutations in mediator complex subunit 12 (MED12). It is a part of the mediator complex, which interacts with RNA polymerase II to regulate gene transcription, which often affected in leiomyomas and other mesenchyme tumors. MED12 interact with both types of estrogen receptors and increase estrogen receptor function in vitro. It can explain the influence of estrogen on fibroid growth enhancement [21].

Histology

The histologic phenotype of LM always different from the adjacent normal myometrium. Most leyomyomata demonstrate much more extracellular matrix deposition than normal myometrium does, and present as encapsulated collagen-rich masses of smooth muscle cells. LM typically have 50% more collagen than normal myometrium and an increased proportion of type I collagen [1]. Another sources revealed that collagen of type III in LM tissue is highly deposed too [20]. Uterine leiomyomas are usually well-circumscribed tumors.

According to the 4th edition of World Health Organization Classification of tumors (Tumors of the Breast and Female genital organs), histologically, leiomyomas are benign neoplasms composed of disorder smooth-muscle cells buried in abundant quantities of extracellular matrix. This pathology is accompanied by changing of myometrial structure and cellular morphology. It were described two types of UL: poor in vessels and rich in vessels.

Grossly, this pathology is multiple, have spherical form, also firm and pale. On section leiomyoma's surface is white to tan in color, with a whorled trabecular texture. This benign tumor cause deformation of surrounding tissues, often with degenerative changes [22].

Microscopically, leiomyomas have whorled, anastomosing fascicles of uni- and fusiform cells. Typically, cells have spindle form, abundant fibrillar, eosinophilic cytoplasm and indistinct borders. Sometimes, particularly in cellular leiomyomas, the cytoplasm is sparse, and the fascicular arrangement of the cells may be muted. Nuclei with small nucleoli and finely dispersed chromatin. Nearby myometrium is less cellular than closed located leiomyomas [3].

Depends on location and size, can be ulcerated, hemorrhagic, with necrotic and cystic degeneration, sometimes become calcified. Hyaline fibrosis, edema and, on occasion, marked hydric change can be present. Haemorrhage, necrosis, oedema, myxoid change, hypercellular foci and cellular hypertrophy occur in leiomyomas in women who are pregnant or taking progestins [23, 24].

In addition, several histological variants of leiomyoma uterus are exist: mitotically active, cellular, haemorrhagic cellular (or "apoplectic"), epitheloid, myxoid, atypical (pleomorphic, bizarre or symplastic) and lipoleiomyoma. Each of them has own characteristics and prognosis. Growth pattern variants may produce unusual clinical, macroscopic and/or histological features. There are four types of growth pattern: diffuse leiomyomatosis, dissecting leiomyoma, intravenous leiomyomatosis and benign metastasizing leiomyoma.

Vascular structure

Uterine fibroids contain their own specific vasculature. Usually following age of 50 uterine arteries are narrowed or even sometimes closed by atherosclerotic obliteration [25]. Vascular architecture is investigated by classical dye-injection methods, as well as by corrosion casting combined with scanning electron microscopy [26].

A unique feature of larger UL is "vascular capsule", which characterized by an extremely dense vascular network at the border between the tumor and the surrounding myometrium,

often separated from the unchanged myometrium by a narrow avascular cleft. The smallest leimyomata are usually avascular. Middle size tumors usually have well-developed vascular capsule and could be occasionally traversed by small vessels (arteries and veins). Large myomata (> 1cm) contain a chaotic network of blood vessels — mostly capillaries, arterioles and venules [18, 26].

Walocha *et al*. distinguished two types of vascularization of intramural UL: a type where peripheral vessels form relatively dense vascular capsule, while the center of the lesion seems to be poorly vascularized and type two, where foci of intensive regression of tumor are separated by strong vascular septa [18, 27].

Genetic

The majority of UL (60%) are chromosomally normal and the remainder share similar tumor-specific abnormalities [2]. Chromosomally abnormal tumors are usually larger and a greater percentage of cytogenetically abnormal fibroids are located submucosally [2, 21]. Genetic changes confined to the tumor tissue and lacking in adjacent myometrial tissue offer a highly valuable tool to shed light on the molecular pathogenesis of the disease. The variety of chromosomal rearrangements, including but not limited to translocation, deletion and trisomy, predict different molecular genetic mechanisms for UL formation and growth [28]. The abnormal karyotypes in leiomyoma were frequently accompanied by 46, XX, i.e., cytogenetically normal female cells [14].

Global gene expression profile of LM revealed that hundreds of genes are deregulated and caused changing in cell proliferation, differentiation and extracellular matrix production [14]. The most often leiomyomas have such genetic abnormalities as deletion of portions of 7q, trisomy 12, rearrangements of 12q15, 6p21 or 10q22. Additional abnormalities, which appear consistently but not as frequently, include rearrangements of chromosomes X, 1, 3 and 13 [28]. The variety of rearrangements suggests that there is more than one molecular pathway leading to leiomyoma tumorogenesis [29].

Few studies showed a positive correlation between the presence of a cytogenetic abnormality and the anatomic location of LM: intramural (35%), subserous (29%) and submucous (12%) type [14, 30]. Analyses of multiple leiomyomas from a single uterus have demonstrated that the tumors can harbor different chromosomal changes and suggest that each tumor can develop independently [14].

One of the most common subgroups is characterized by rearrangement of 12q14-15, typically as a t(12;14)(q14-15;q23-24), which occurs in approximately 7.5% of all leiomyomas and 20% of karyotypically abnormal leiomyomas [8, 31]. Most of the 12q15 breakpoints are located upstream of the HMGA2 gene promoter, giving rise to full-length HMGA2 overexpression [8]. The presence of t(12;14) has been associated with larger sized UL than those with either normal karyotypes or interstitial 7q22 deletions [14, 28, 30, 31].

One of the largest UL subgroups is defined by the presence of chromosome 7 long arm abnormalities, most commonly the interstitial deletion del(7)(q22q32), which represents approximately 15% of all UL and 20–35% of karyotypically abnormal UL. It is notable that UL with 7q abnormalities are often mosaic with karyotypically normal 46,XX cells and when

cultured grow poorly and frequently lose the chromosomally aberrant cell line [21]. Tumors with del(7) were found to be smaller and those with mosaic karyotypes were intermediate in size [14, 32]. In addition, del(7) may be associated with t(12;14) or t(1;6), suggesting involvement of del(7) in the karyotypic evolution of leiomyoma [14].

Rearrangements of 6 chromosome in band 21 in leiomyoma occur with a frequency of 5% and include t(1;6)(q23;p21), t(6;14)(p21;q24), and t(6;10) (p21;q22), as well as inversions and translocations with other chromosomes [14].

About 5% of chromosomally abnormal uterine leiomyomata had rearrangements of 10q22 [29]. This region is implicated in a wide variety of tumors, with a number of tumor suppressor genes including PTEN/MMAC1 (at 10q23.3) and DMBT1 (at 10q25.3-q26.1) [1, 14].

Genetic studies of uterine leiomyomas from a variety of populations have demonstrated translocations in the high mobility group (HMG) protein genes, specifically HMGA1 and HMGA2. Aberrant expression of HMGA2 may affect the expression of growth factors and growth inhibitors, fibroblast growth factor 2 (FGF2) and p19 alternate reading frame ($p19^{Arf}$), respectively. Moreover, the overexpression of HMGA2 in leiomyomas correlates with increased FGF2 levels and tumor size, and repression of the growth inhibitor factor $p19^{Arf}$ [16].

There is also a genomewide difference in DNA methylation between the fibroid tissue and the adjacent normal myometrium. Promoter methylation-mediated gene silencing might be involved in pathogenesis of leiomyomas [8, 13].

As expression and deposition of ECM and collagens are common for leiomyomata, will be important note some facts about its gene regulation. Studies were found significant differential expression of dermatopontin (DPT) and various isoforms of the fibrillar (I, III, V) and nonfibrillar collagen genes (IV and VI) in leiomoyoma compared to myometrium [33].

Hereditary syndromes

UL may be a component of several hereditary syndromes. For instance, hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) is an autosomal dominant disease (also known as Reed's syndrome), characterized by aggressive early-onset renal cancer combined with multiple leiomyomas of skin and uterus. Patients with HLRCC have a deficiency of the fumarate hydratase. About 77 percent women with this syndrome have uterine leiomyomas, that early appears and are multiple with size ranging from 1 to 8 cm. Also, they are usually highly symptomatic. Histologically, these tumors oftentimes have increased cellularity and nuclear atypia. Usually, patients with HLRCC have cellular or atypical variants of leiomyomas [2, 4, 24, 34–36].

Alport syndrome, caused progressive nephropathy and connected with a defect in COL4A5 and COL4A6 genes, include rare clinical condition — diffuse leiomyomatosis. It's characterized by benign smooth-muscle cell proliferation in the female genital tract. Diffuse leiomyomatosis concerns approximately 5% of patients with Alport syndrome [2].

One more example of combination leiomyomas with hereditary syndromes is Recklinghausen's disease (Neurofibromatosis type 1 (NF1)). It is one of the most frequent human genetic diseases, with a prevalence of one case in 3,000 births. The literature suggests that the association of NF1 and leiomyomas or leiomyosarcoma is not entirely coincidental [37].

Growth factors

Many uterine growth factors are regulated by sex steroids, which effect through local modulation of growth factors, cytokines and chemokines. The autocrine/paracrine signaling plays an important role in the events involved in myometrium cellular transformation and turnover that are involved in leiomyoma pathophysiology [21, 22].

Recently proved that several growth factors and their respective receptors seem to play a role in leiomyoma growth. The main of them are: inslulin-like growth factors (IGFs), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VRGF), epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF), heparin binding epidermal growth factor (HB-EGF), tumor necrosis factor-α (TGF-α), transforming growth factor beta (TGF-β), acidic fibroblast growth factor (aFGF) and adrenomedullin (ADM). Some of them involved in angiogenesis in leiomyoma, others can modulate the rate of cell proliferation or regulate gene expression. For instance, TGF-β is a potent promoter of connective tissue formation [1, 8, 21, 22, 38].

PDGF modulate the rate of cell proliferation in myometrium and leiomyoma cells and probably play a role in SMC hypertrophy as its expression is increased in myometrium during gestation, while decreasing of PDGF associated with shrinkage of uterine volume [1, 13]. Also, this growth factor is upregulated by estrogen in uterine SMC and downregulted by GnRH agonists. PDGF may interacts with other growth factors such as TGFβ and EGF to enhance proliferation [22]. EGF and PDGF seem to increase DNA synthesis and polyploidization in leiomyoma cells through transient activation of kinase pathways [7, 13].

bFGF mRNA and protein are present in myometrial and leiomyoma smooth muscle cells, with higher level in leiomyoma cells. Leiomyoma tissue has an extensive ECM with heparin sulfate proteoglycans that serves as a reservoir for bFGF. Several researchers reported the expression of bFGF and its receptors FGFR-1 and FGFR-2 in both leiomyoma and leiomyoma cells, with more distinct expression of FGFR-1 in the tumors compared with myometrium [21, 22].

HB-EGF is a strong mitogen for both fibroblasts and smooth muscle cells. Shows a decreased expression in leiomyomas relative to normal myometrium. Progesterone increase its expression in the uterine stroma and decreases in luminal and glandular epithelium. Estradiol increases HB-EGF in epithelial cells and has no effect on stromal cells. mRNA and protein amounts are lower in leiomyoma smooth muscle cells compared with normal myometrium [20, 21].

No differences in VEFG protein expression have been detected between normal myometrium and leiomyoma tissue. Another studies revealed a stronger VEGF expression was found in leiomyomas than in adjacent myometrium, indicating the local angiogenesis may be important for the development and growth of tumor tissue. Interestingly, that VEGF is significantly expressed in leiomyosarcoma compared with leiomyoma [21, 22].

Recently has been demonstrated that EGF plays a crucial role as a local growth factor in regulating leiomyoma growth. EGF and EGF receptor mRNA are both highly expressed in normal myometrium and leiomyoma smooth muscle cells. The level of EGF mRNA is higher in leiomyomata during the secretory phase. Progesterone increases EGF expression

and mitogenesis of cultured smooth muscle cells. Were found that asoprisnil (J867), a novel selective P_4 receptor (PR) modulator down-regulated expression of EGF and its receptors in cultured uterine leiomyoma cells without altering EGF-induced proliferation and apoptosis rates in normal myometrium. Estrogen treatment reduces EGF expression but upregulates the expression of EGF-R and proliferative cell nuclear antigen (PCNA), an endogenous marker of cell proliferation, in both myometrium and leiomyoma cells [22].

TGF-β and its receptors are expressed in human myometrium and leiomyomas. Their role on leiomyoma pathogenesis has been hypothesized because TGF-βs, their receptors and downstream signaling mediators are overexpressed in UL compared with normal myometrium. Leiomyomas express up to six fold higher levels of mRNA for TGF-β3 than do normal myometrial cells at all stages of the menstrual cycle [14]. When TGF-β is downregulated, the mRNA expression of multiple ECM genes in tumor is decline [13, 22].

Some studies reveal that IGFs and their signaling pathways are activated in approximately one third of fibroids and that IGF signaling is positively associated with large and actively growing fibroids. They regulate cell proliferation, differentiation and apoptosis. There are two IGFs: IGF-1 and IGF-2.Over-expression of IGF-2 in LM has been identified in many independent global gene profiling analysis. Although IGF-1 transcription can be promoted by estrogen in both normal and tumor tissue, only a portion of fibroids (about one third) have its increased level (particularly in large LM) [22, 38].

Adrenomedullin belongs to the calcitonin superfamily of peptides that includes calcitonin, calcitonin gene-related peptide (CGRP) and amilyn. This substance manifests as an inhibitor of apoptosis and an autocrine growth factor in several human cancer cell lines and endometrium. The ADM is an important angiogenic factor in smooth muscle tumor of uterus. ADM protein expression has been reported in both myometrium and leiomyoma tissue, where it is significantly higher. Although, it can be used as an accessory marker in estimating the malignant potency of UL and judging the prognosis of uterine leiomyosarcomas, and as a novel molecular target of anti-angiogenic and anticarcinogenic strategies [21, 39].

Among the angiogenic factors, bFGF and AMD are the likely candidates to promote angiogenesis around myomata, since they were found to occur in larger quantities in myomata than in the unchanged myomatrial areas [26].

Hormones and its receptors

Numerous experiments have shown that combination of estrogen and progesterone promote myometrial and leiomyoma smooth muscle cells growth. They regulate most of genes that encode growth factors.

UL growth is related to estrogens and their receptors. Estrogen receptors consist of ERα and ERβ. Leiomyomata and myometrium expressed both types of receptors. Several studies found that mRNA and protein expression levels are higher in leiomyomara compare to those in normal myometrium [13]. Different studies present dual judgment about expression of both types of estrogen receptors in leiomyomas. One of them demonstrate significantly higher expression of ERα as compared of ERβ in the tumor. Others show opposite results and justified possible involvement expression ratio in the growth potential of leiomyomas.

Estrogens can regulate the expression of growth factors by acting some signaling pathways. They upregulate PDGF expression in fibroid cells and downregulate EGF expression, while upregulate the expression of EGF-R in both myometrium and leiomyoma cells [7].

Progesterone and its receptors are essential for cell proliferation, the accumulation of extracellular matrix, and cellular hypertrophy. Their expression (PR-A and PR-B) is significantly higher in leiomyoma tissue compared with normal myometrium. Progesterone has an impact on some growth factors. It upregulates the EGF (mitogenic) and TGF-β3 (bimodal action) expression. Likewise, it seems to downregulate IGF-I expression. Hypothetically, progesterone could stimulate leiomyoma cell growth through upregulating B-cell lymphoma 2 (Bcl-2) protein expression and downregulating TNF-α expression [13].

Human uterine leiomyomata express higher levels of peroxisome proliferator-activated receptor γ, retinoid X, and all-trans retinoic acid than myometrium [40].

Cytokines and chemokines

The expression of many cytokines is also regulated by ovarian steroids. Among the major cytokines the expression of IL-1, IL-6, IL-11, IL-12, IL-15, IFNγ, TNF- α, CM-CSF, and erythropoietin has been documented in UL, with limited evidence of their biological involvement in leiomyoma pathophysiology [1]. However, IL-11 and IL-13 similar to TGF-β, are overexpressed in leiomyomata, and differentially regulated by estrogen, progesterone, GnRHa, and TGF-β. Chemokines and their receptors (MIP-1α, MIP-1β, RANTES, eotaxin, eotaxin-2, IL-8, CCR1, CCR3, CCR5, CXCR1 and CXCR2 mRNA) are also play role in pathogenesis of leiomyoma. Leiomyoma tissue has a lack of IL-8, IL-8, MCP-1 and MCP-2 compare with normal myometrium [13].

Model systems

Researchers may studying in details mechanisms underlying UL growth regulation and others features by creating artificial models (human and animals). Had been distinguish three types of models: in vitro, in vivo and stem cells models. In vitro were created such systems as human uterine leiomyoma cells (2008, 2010, 2012), Htert-human uterine leiomyoma cells (2012), 3D *in vitro* model (2012) and Eker leiomyoma tumor-derived (ELT) 3 cells (2010). Wider range of models in vivo are presented and they are mostly animals: Eker rat (2009, 2011), Guinea pig (1989), Miniature pet pigs (2010), Pot bellied pig (2004), Japanese quail (2009), CD-1 mice (2002), Calcium-binding protein (CaBP) 9K/Tag^{J} transgenic mice (1996), Transplanted fibroid cells in mice (xenografts) (2009, 2010), Immunodeficient (NOD/SCID/gammac(null): NOG) mice (2010), Adenovirus-enhanced human fibroid explants (2008) and Beta-catenin mice (2009). Two stem cells systems available for modeling of pathological condition: Human uterine leiomyomas (2010) and Leiomyoma-derived side population (LMSP) stem/reservoir cells (2012) [11, 16].

The most widely used is Eker rat model in which approximately 65% of female Tsc2$^{Ek/+}$ carriers develop leiomyomas, a frequency similar to that seen in women. This model has similar phenotypic, biochemical, hormonal and genetic characteristics compare with cognate

human pathology. Approximately 8% of aged guinea pigs develop spontaneous leiomyomas, and ovariectomy in young animals combined with high-dose estrogen supplementation causes the development of uterine and abdominal leiomyomas with a high frequency. Both models have a common result, which suggest that selective estrogen modulators and peroxisome proliferator-activator receptors ligands may be effective as therapeutic agents [11].

A xenograft model showed that removal of steroid hormones associate with decreasing tumor size and reducing cell size. Moreover, it proved depending of progesterone receptors form estrogen in UL [16].

Symptoms

The majority of women with UL are asymptomatic, consequently get less clinical attention and fibroid tumors often remain undiagnosed [41]. Prevalence in symptom-free women has been reported to be as low as 7.8% in Scandinavian women aged 33 to 40, whereas in the United States it is almost 40% in white patients and more than 60% in women of African ancestry in the same age group [19]. Symptoms are often depends on size, localization and numbers of fibroids. The clinical presentation can be divided into three main groups of symptoms: abnormal bleeding, pressure/pain, and reproductive problems.

Usually leiomyomata are often highly vascularized (especially in the pseudocapsule) and frequently associated with menorrhagia. One study revealed that 30% of the patients had this complication. The range varied from 17 to 62%. After menorrhagia, the most common abnormal bleeding symptom is prolonged vaginal bleeding. Usually it is occur during submocous leiomyoma because fibroid destroy the endometrial cavity [1].

As leiomyoma is tissue which can growing outside, it can mechanically push on surrounding organs and nerves, accompanying by subjective feeling of heaviness, pressure, or dull ache but rarely pain. The size and localization of UL may affect the pressure and pain experienced. Frequently, these symptoms combine with others and create a complex of disorders. Anterior leiomyomata may cause urinary symptoms, while posterior — constipation.

Occasionally acute pain may be associated with leiomyomata. In addition, pain can be a symptom of fibroid degeneration (usually necrosis). In literature, present data of one study depict that 42% of women with chronic pain requiring laparoscopy had leiomyomata [1, 8].

Leiomyoma can be a reason of infertility. The incidence of UL in women with unexplained infertility is estimated to be 1 to 2.4%. It can be caused by distortion of the endometrial cavity, obstruction of uterine tubes or cervix, alteration of endometrium, vascular changes which discommode to implantation. Moreover, submucous fibroids seems to be a reason of infertility. They are accompanied by decreasing of markers of endometrial receptivity (HOXA10, HOXA11 and BTEB1) and lower concentrations of glycodelin and interleukin 10 in mid-luteal phase in the endometrium [42]. Likewise, leiomyoma may interfere with sperm migration and embryo transport by modifying the normal uterine contractility [43].

Subserous and submucosal fibroids slightly increased the risk of pre-term birth. The majority of women with uterine fibroids will have normal pregnancy outcomes [16].

Sarcomatous change in leiomyomata is rare and it thought to occur in no more than 0.1% of leiomyomata. It is more common in postmenopausal women and can present with

bleeding or pain associated with uterine enlargement. Sometimes single cases with hypothesis of cancer transformation of UL are published, but they are still discussable [1].

Diagnosis

In general, patients with leiomyoma will come to doctor with complaints of abnormal bleeding or infertility. The diagnosis can include vaginal examination, ultrasound, hysteroscopy and magnetic resonance imaging (MRI). Clinical examination is accurate with a uterine size of 12 weeks (correlating with a uterine weight of approximately 300 g) or larger. Ultrasonography is helpful to observe size, localization, numbers, structure, relation to the endometrial cavity of fibroid and assess the adnexa if these can't be palpated separately with confidence [44]. Moreover, it may be essential in differential diagnosis between several gynecological pathologies, which might be suspected. For instance, some parameters of blood flow impedance of arteries within or around the uterine lesions revealed a consistent and significant difference between leiomyoma and adenomyosis, made by Doppler [1, 45].

Treatment

Symptoms that negatively affect a woman's daily life are a primary indication for treatment. Standard treatments of LM symptoms include myomectomy, hysterectomy, uterine artery embolization, and pharmacologic treatments that reduce symptoms.

Myomectomy has been the mainstay for women who wish to preserve their fertility. It can be done by laparotomy or laparoscopy. Vaginal myomectomy is the classical method for cervical leyimyomata and pedunculated submucosal UL. Hysterectomy can be carried out abdominally, vaginally, or laparoscopically. A large-scale surveys have shown that 70–80% of hysterectomies are performed by the abdominal approach, especially in the case of uterine leiomyomata [1].

For patients with asymptomatic uterine myomas, surgery was determined in which 1) the size of tumor was bigger than 6 cm, 2) if a request was made by a patient with cancer phobia, and 3) a surgeon determined to do so [46].

Uterine artery embolization (UAE) has proven to be a well-tolerated, minimally invasive treatment for symptomatic uterine fibroids. Its aim is the reduction or elimination of fibroid-related symptoms, but not the removal of the leiomyoma. However, it also accomplishes a reduction of the size of the fibroid. A symptomatic uterine fibroid is an indication for uterine artery embolization.

Outcome

Study, provided in USA in 2010, compare different kinds of surgical treatment in cases of leiomyoma and its outcomes. The frequency of adverse events was similar among the groups (6.7% of uterine artery embolization, 13.3% of myomectomy, and 13.3% of hysterectomy) [47].

Another study observe patients with LM and infertility (primary and secondary) after surgical treatment. Pregnancy outcome confirmed the validity of the laparoscopic approach.

Approximately 55% of the infertile women who underwent surgery achieved pregnancy. The reappearance of UL during the follow-up period was similar in the two groups (22.3% after laparotomy; 21.4% after laparoscopy) and, considering only large leiomyomata, the recurrence rates were 6.7% (laparotomy) and 1.8% (laparoscopy) respectively [43].

Conflict of interest

None declared.

References

1. *Brosens I.*: Uterine Leiomyomata: Pathogenesis and Management. Abingdon, England, Informa Healthcare/Taylor & Francis, 2006.
2. *Levy G., Hill M., Beall S., Zarek S., Segars J., Catherino W.*: Leiomyoma: Genetics, assisted reproduction, pregnancy and therapeutic advances. Journal of Assisted Reproduction and Genetics. 2012; 29 (8): 703–712.
3. *Tavassoli F., Schnitt S., Hoefler H., Boecker W., Rosai J., Heywang-Kobrunner S.H., et al.*: Intraductal proliferative lesions. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. 2003; Vol. 4.
4. *Laughlin S., Stewart E.*: Uterine Leiomyomas: Individualizing the Approach to a Heterogeneous Condition. Obstet Gynecol. 2011; 117 (2 Pt 1): 396–403.
5. *Stewart E.A.*: Uterine fibroids. N Engl J Med. 2015; 372: 1646–1655.
6. *Bozini N., Baracat E.C.*: The history of myomectomy at the Medical School of University of São Paulo. Clinics (Sao Paulo, Brazil). 2007; 62 (3): 209–210.
7. *Borahay M., Al-Hendy A., Kilic G.S., Boehning D.*: Signaling Pathways in Leiomyoma: Understanding Pathobiology and Implications for Therapy. Molecular Medicine (Cambridge, Mass.). 2015.
8. *Bulun S.E.*: Uterine Fibroids. The New England Journal of Medicine. 2013; 369 (14): 1344–1355.
9. *Ishikawa H., Reierstad S., Demura M., Rademaker A.W., Kasai T., Inoue M., et al.*: High aromatase expression in uterine leiomyoma tissues of African-American women. Journal of Clinical Endocrinology and Metabolism, 2009; 94 (5): 1752–1756.
10. *Mitro S.D., Zota A.R.*: Vitamin D and uterine leiomyoma among a sample of US women: Findings from NHANES, 2001–2006. Reproductive Toxicology. 2015; 25: 2001–2006.
11. *Walker C.L., Stewart E.*: Uterine fibroids: the elephant in the room. Science (New York, N.Y.). 2005; 308 (5728): 1589–1592.
12. Stanowisko Zespołu Ekspertów Polskiego Towarzystwa Ginekologicznego w sprawie zastosowania selektywnych modulatorów receptora progesteronowego (SPRM) w leczeniu mięśniaków macicy. Ginekologia Polska. 2012; 83: 555–557.
13. *Ciavattini A., Di Giuseppe J., Stortoni P., Monti N., Giannubilo S.R., Litta P., et al.*: Uterine fibroids: pathogenesis and interactions with endometrium and endomyometrial junction. Obstetrics and Gynecology International. 2013; 173–184.
14. *Medikare V., Kandukuri L.R., Ananthapur V., Deenadayal M., Nallari P.*: The genetic bases of uterine fibroids; a review. Journal of Reproduction and Infertility. 2011; 12 (3): 181–191.
15. *Moravek M.B., Yin P., Ono M., Coon J.S. Vth, Dyson M.T., Navarro A., et al.*: Ovarian steroids, stem cells and uterine leiomyoma: therapeutic implications. Human Reproduction Update. 2014; 21 (1): 1–12.
16. *Segars J.H., Parrott E.C., Nagel J.D., Guo X.C., Gao X., Birnbaum L.S., et al.*: Proceedings from the third national institutes of health international congress on advances in uterine leiomyoma research: Comprehensive review, conference summary and future recommendations. Human Reproduction Update. 2014; 20 (3): 309–333.

17. *Faerstein E., Szklo M., Rosenshein N.*: Risk Factors for Uterine Leiomyoma: A Practice-based Case-Control Study. American Journal of Epidemiology. 2001; 153 (1): 1–10.
18. *Bereza T., Lis G., Mitus J., Sporek M., Chmielewski P., Kolber W., Mazur M., Goncerz G., Kuniewicz M.*: Blood vessels of the intratumoral septa in uterine leiomyomata. Folia Med Cracov. 2013; 53 (2): 99–106.
19. AAGL Practice Report: Practice, Guidelines for the Diagnosis and Management of Submucous Leiomyomas. Journal of Minimally Invasive Gynecology. 2012; 19 (2): 152–171.
20. *Koohestani F., Braundmeier A., Mahdian A., Seo J., Bi J., Nowak R.*: Extracellular matrix collagen alters cell proliferation and cell cycle progression of human uterine leiomyoma smooth muscle cells. PloS One. 2013; 8 (9).
21. *Tal R., Segars J.*: The role of angiogenic factors in fibroid pathogenesis: Potential implications for future therapy. Human Reproduction Update. 2014; 20 (2): 194–216.
22. *Ciarmela P., Islam S., Reis F., Gray P.C., Bloise E., Petraglia F., et al.*: Growth factors and myometrium: Biological effects in uterine fibroid and possible clinical implications. Human Reproduction Update. 2011; 17 (6): 772–790.
23. *Lynch A., Morton C.*: Uterus: Leiomyoma. Atlas of Genetics and Cytogenetics in Oncology and Haematology. 2011; 12 (1): 68–73.
24. *Rackow B.W., Taylor H.S.*: Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. Fertil Steril. 2010; 93 (6): 2027–2034.
25. *Bereza T., Tomaszewski K., Skrzat J., Klimek-Piotrowska W., Sporek M., Mizia E., Lis G., Pasternak A.*: Quality of corrosion specimens prepared from material obtained during autopsies — a preliminary study. Folia Med Cracov. 2013; 53 (1): 5–12.
26. *Walocha J.A., Litwin J.A., Miodoński A.J.*: Vascular system of intramural leiomyomata revealed by corrosion casting and scanning electron microscopy. Hum Reprod. 2003; 18 (5): 1088–1093.
27. *Walocha J., Miodoński A.J., Szczepański W., Skrzat J., Stachura J.*: Two types of vascularisation of intramural uterine leiomyomata revealed by corrosion casting and immunohistochemical study. Folia Morphol. 2004; 63 (1): 37–41.
28. *Hodge J., Morton C.*: Genetic heterogeneity among uterine leiomyomata: Insights into malignant progression. Human Molecular Genetics. 2007; 16: 7–13.
29. *Moore S.D.P., Herrick S.R., Ince T., Kleinman M, Cin P.D., Morton C.C., Quade B.J.*: Uterine leiomyomata with t (10; 17) disrupt the histone acetyltransferase MORF. Cancer Research. 2004; 64 (16): 5570.
30. *Flake G.P., Andersen J., Dixon D.*: Etiology and pathogenesis of uterine leiomyomas: A review. Environmental Health Perspectives. 2003; 111 (8): 1037–1054.
31. *Hodge J., Kim T., Dreyfuss J., Somasundaram P., Christacos N., Rousselle M., et al.*: Expression profiling of uterine leiomyomata cytogenetic subgroups reveals distinct signatures in matched myometrium: Transcriptional profilingof the t(12;14) and evidence in support of predisposing genetic heterogeneity. Human Molecular Genetics. 2012; 21 (10): 2312–2329.
32. *Hennig Y., Deichert U., Bonk U., Thode B., Bartnitzke S., Bullerdiek J.*: Chromosomal translocations affecting 12q14-15 but not deletions of the long arm of chromosome 7 associated with a growth advantage of uterine smooth muscle cells. Molecular Human Reproduction. 1999; 5 (12): 1150–1154.
33. *Davis B.J., Risinger J.I., Chandramouli G.V.R., Bushel P.R., Baird D.D., Peddada S.D.*: Gene Expression in Uterine Leiomyoma from Tumors Likely to Be Growing (from Black Women over 35) and Tumors Likely to Be Non-Growing (from White Women over 35). PLoS ONE. 2013; 8 (6).
34. *Jason J., Solomon S., Mercer E.S.*: Reed's Syndrome A Case of Multiple Cutaneous and Uterine Leiomyomas. J Clin Aesthet Dermatol. 2011; 4 (12): 37–42.
35. *Kiuru M., Launonen V., Hietala M., Aittomäki K., Vierimaa O., Salovaara R., et al.*: Familial cutaneous leiomyomatosis is a two-hit condition associated with renal cell cancer of characteristic histopathology. The American Journal of Pathology. 2001; 159 (3): 825–829.
36. *Wollina U., Schönlebe J.*: Reed' s syndrome : segmental piloleimyomas type 1 and uterus myomatosus. Journal of Dermatological Case reports. 2014; 67–69.

37. *Kluger N., Perrochia H., Guillot B.*: Pelvic mass in von Recklinghausen's neurofibromatosis: diagnostic issues: a case report. Cases Journal. 2009; 2: 191.
38. *Peng L., Wen Y., Han Y., Wei A., Shi G., Mizuguchi M., et al.*: Expression of insulin-like growth factors (IGFs) and IGF signaling: molecular complexity in uterine leiomyomas. Fertility and Sterility. 2009; 91 (6): 2664–2675.
39. *Jiang Y., Tian X., Yuan J., Jin Y., Tan Y.*: Relationship of adrenomedullin expression and microvessel density and prognosis in smooth muscle tumor of uterus. Front Med China. 2007; 1 (4): 398–400.
40. *Bereza T., Skrzat J., Szczepanski W., Mitus J., Tomaszewski K., Depukat P.*: Vascular structure of outer myometrial uterine leiomyomata — a preliminary SEM and immunohistochemical study. Folia Med Cracov. 2013; 53 (1): 23–30.
41. *Zimmermann A., Bernuit D., Gerlinger C., Schaefers M., Geppert K.*: Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Women's Health. 2012; *12*: 6. doi:10.1186/1472-6874-12-6.
42. *Makker A., Goel M.*: Uterine leiomyomas: effects on architectural, cellular, and molecular determinants of endometrial receptivity. Reproductive Sciences (Thousand Oaks, Calif.). 2013; 20 (6): 631–638.
43. *Seracchioli R., Rossi S., Govoni F., Rossi E., Venturoli S., Bulletti C., Flamigni C.*: Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. Human Reproduction (Oxford, England). 2000; 15 (12): 2663–2668.
44. *Casali P.G., Jost L., Reichardt P., Schlemmer M., Cutsem E. Van, Oliveira J.*: Clinical Recommendations. Annals of Oncology. 2009; 20 (Supplement 4): 2008–2010.
45. *Sharma K.*: Role of 3D Ultrasound and Doppler in Differentiating Clinically Suspected Cases of Leiomyoma and Adenomyosis of Uterus. Journal of Clinical and Diagnostic Research. 2015; 9 (4): 8–12.
46. *Jeong J., Kim Y., Kim E., Moon S., Park M., Kim, J. et al.*: Comparison of Surgical Outcomes according to Suturing Methods in Single Port Access Laparoscopic Myomectomy. 2015: 47–55.
47. *Spies J.B., Bradley L.D., Guido R.*: Outcomes from leiomyoma therapies: comparison with normal controls. Obstet Gynecol. 2010; 116 (3): 641–652.