PATHOGENETIC ASPECTS OF UTERINE FIBROIDS (REVIEW OF LITERATURE)

Kochieva A.M.
Tashkent Pediatric Medical Institute
https://doi.org/10.5281/zenodo.11410588

Abstract. *Uterine fibroids consistently occupy a leading position in the structure of gynecological pathology and have a significant impact on a woman's reproductive function, while the etiology and pathogenesis of the disease are the subject of debate. This article provides an analysis of modern literature on the problem of etiopathogenesis of uterine fibroids.*
Keywords*: uterine fibroids, endometrium, marker.*

Uterine leiomyomas (UL), commonly known as myomas, are noncancerous tumors arising from the myometrium (smooth muscle layer) of the uterus. In addition to smooth muscle, leiomyomas are also composed of extracellular matrix (collagen, proteoglycan, fibronectin). Leiomyomas are the most common solid pelvic tumor in women, causing symptoms in approximately 25% of women of reproductive age. But with careful uterine pathologic examination, the overall prevalence of leiomyoma increases to more than 70% because many women may have leiomyomas without symptoms. Leiomyomas are usually detected in women between 30 and 40 years of age and decrease after menopause in the absence of postmenopausal estrogen replacement therapy [1].

Leiomyomas result from overgrowth of smooth muscle and connective tissue of the uterus (2). There are two components of myoma development; first there is the transformation of normal myocytes into abnormal myocytes and their growth into clinically distinct tumors. In addition to their oncogenic potential, they are morphologically similar at the cellular level to normal myometrial smooth muscle cells (MSMC). Leiomyomas may have solitary or multiple mutated smooth muscle tumor nodules of varying size, attached to or within the myometrium, surrounded by varying amounts of extracellular fibrous connective tissue. Microscopic studies show that they have interlacing bundles of spindle-shaped or stellate smooth muscle cells with little cellular pleomorphism or mitotic activity [1,3].

The identity of the factors and molecular mechanisms involved in the cellular transformation of myometrial cells to leiomyoma remains unknown. There is also evidence to support the involvement of genomic instability affecting genes such as estrogen and progesterone receptors. Several genomic and proteomic studies have also provided evidence of an altered molecular environment of leiomyoma compared to normal myometrium, which is a possible biomarker of their proliferation and regression [4].

Global gene expression profiling of uterine leiomyoma (ULM) has shown that hundreds of genes are disrupted, including those that play a functional role in cell proliferation, cell differentiation, and extracellular matrix production. To date, only a few specific genes or cytogenetic aberrations associated with (ULM) have been identified. Although many of the unregulated genes may function as effectors or promoters of ULM growth, they are likely to be secondarily induced and indirectly responsible for tumor growth into pathological and symptomatic ULM [5].

There is a suggestion of a small increase in myoma risk associated with early menarche [7-9]. Early onset of menstrual cycles may increase the number of cell divisions to which the myometrium undergoes during the reproductive period, leading to an increased risk of mutations in genes controlling myometrial proliferation [10-12].

Theories of myoma formation

Despite the serious public health impact of leiomyomas, little is known about their causes. The most important aspect of myoma etiology, the initiators, remains unknown. Several theories have been proposed. One hypothesis states that increased levels of estrogen and progesterone lead to increased mitosis rates, which may contribute to myoma formation by increasing the likelihood of somatic mutations [15]. Another suggests the presence of congenital abnormalities of the myometrium in people with uterine myoma, based on the finding of significantly elevated levels of estrogen receptors (ER) in the myometrium of myoma uteri [6-9].

More recently, growth factors have been shown to mediate the growth-promoting effect of estrogen and play an important role in the development of tumor myoma [1]. Growth factors, protein-polypeptides produced locally by smooth muscle cells and fibroblasts, control cell proliferation and appear to stimulate myoma growth primarily by increasing extracellular matrix. Some of the identified growth factors associated with myoma are transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF) and prolactin [16].

Growth factors affect cells in complex ways, and the response to combinations of growth factors may differ from the response to a single factor. Many of these growth factors are overexpressed in myomas and either increase smooth muscle proliferation (TGFβ, bFGF), increase DNA synthesis (EGF, PDGF), stimulate extracellular matrix synthesis (TGF-β), promote mitogenesis (TGF-β, EGF, IGF, prolactin), or promote angiogenesis (bFGF, VEGF) [16]

The steroid hormones estrogen and progesterone are considered the most important regulators of leiomyoma growth.

There is abundant evidence that estrogen promotes myoma growth, including clinical observations that myomas grow at high estrogen levels, such as during reproductive age, or regress at low estrogen levels, such as after menopause or during therapy with gonadotropin-releasing hormone (GnRH) agonists [12].

In addition, because the risk of myoma development is higher in unbearing women, who may have a higher frequency of anovulatory cycles, and in obese women, in whom androgens are more likely to be aromatized into estrone in adipose tissue, the concept of insurmountable estrogen exposure as a major cause of uterine myoma dysfunction has been proposed in the literature [16-18].

The increased myoma growth among women taking tamoxifen or receiving transdermal or injectable estrogen replacement therapy further confirms the importance of estrogen. The estrogen hypothesis has also been supported by clinical trials evaluating drug treatment of myoma with, GnRH agonists with the effective result of hypoestrogenism accompanied by myoma regression [19].

Progesterone is thought to play a role in myoma growth, which is supported by clinical studies. For example, myoma size increases during treatment with synthetic progesterones. In contrast to GnRH agonist therapy, which has been shown to reduce uterine volume, the

combination of GnRH agonist and progesterone therapy has been shown to have no effect on uterine volume. The observation that myoma regressed when the anti-progesterone agent RU-486 was administered further supports the role of progesterone as a promoter of myoma growth. Histologically, myomas in patients treated with progesterone demonstrate greater cellular growth than in patients without progesterone. [17].

Analyses of multiple leiomyomas from a single uterus have shown that the tumors may contain different chromosomal changes and suggest that each tumor may develop independently. Studies of

X-inactivation based on the phenomenon of lyonization, i.e., inactivation of a single X chromosome in normal female cells, have demonstrated that leiomyomas develop as clonal lesions. Initially, glucose-6-phosphate dehydrogenase (G6 PD) isoenzyme analysis was used to demonstrate the independent clonal origin of multiple tumors in a single uterus [7]. Another, more informative approach based on CAG repeat polymorphism in the X-linked androgen receptor gene was used to study clonality, and the results confirmed the monoclonal nature of leiomyoma. A study of a patient with two independent leiomyomas, each showing a different pattern of X chromosome inactivation but with identical derived chromosomes del(7)(q21.2q31.2), supports the view that identical cytogenetic changes in multiple leiomyomas of the same origin The patient may have recurrent chromosomal aberrations in smooth muscle or they may be incidental. Cytogenetically mosaic tumors have also been reported to be clonal [20].

X-linked phosphoglycerokinase (PGK) inactivation studies showed that all leiomyomas studied had one type of inactive allele and were of single-cell origin, but were independently generated in utero. Based on the monoclonal inactivation pattern of X-karyotypically normal leiomyoma cells, Mashal et al. suggested that these cells are part of a tumor clone and that clonal expansion of tumor cells may precede the development of cytogenetic changes in some leiomyomas. [20].

The discovery of heterogeneity in chromosomal aberrations is consistent with the multistage hypothesis of tumor development, according to which the function (or dysfunction) of several genes at multiple loci leads to myoma growth. Abnormalities at multiple loci have been reported in individual tumors, and this heterogeneity may explain the clinicopathologic differences observed in myomas, including differences in size or response to hormonal treatment. [21].

Cytogenetic studies

Standard karyotyping was used to detect chromosomal aberrations such as deletions, duplications, and translocations that require culture of leiomyoma cells to obtain metaphase preparations

An alternative method that has been used in several studies [22, 23]. is comparative genomic hybridization, which allows the recognition of cytogenetic changes such as deletions and amplifications without the need for cell cultures, although it does not allow the detection of balanced rearrangements. Neither standard karyotyping nor comparative genomic hybridization can detect small submicroscopic chromosomal abnormalities such as point mutations or epigenetic changes such as methylation [24].

Approximately 40% of patients with CL have non-random and tumor-specific chromosomal abnormalities. This has allowed classification of some UL into well-defined subgroups that include deletion of parts of 7q, trisomy 12, or rearrangements of 12q15, 6p21, or 10q22. Additional abnormalities that appear consistently but less frequently include

rearrangements of chromosomes X, 1, 3, and 13. The diversity of chromosomal rearrangements, including but not limited to translocation, deletion, and trisomy, predicts different molecular genetic mechanisms for UL formation and growth. (24). The tendency of karyotypically abnormal leiomyomas to be more cellular and have a higher mitotic index than chromosomally normal tumors has been reported (16).

Although no association between patient age or parity and type of chromosomal abnormality was found, several studies have found a positive correlation between the presence of cytogenetic abnormality and the anatomic location of uterine leiomyoma, i.e., intramural (35%) and subserosal (29%) leiomyomas are more likely to have abnormal karyotypes than submucosal (12%). Another study showed a correlation between karyotype and leiomyoma size, with the largest tumors carrying abnormal t(12;14). In contrast, tumors with del(7) were smaller in size, and tumors with mosaic karyotypes were of intermediate size [1, 5, 7, 11].

Abnormal karyotypes in leiomyoma were often accompanied by 46, XX, that is, cytogenetically normal female cells. Although this may represent concomitant growth of normal cells, it is possible that these apparently normal cells may have undergone neoplastic transformation with the appearance of chromosomal changes after this transformation [26].

The most common chromosomal aberration in leiomyoma, observed in approximately 20% of karyotypically abnormal leiomyomas, is a characteristic t(12;14) (q15;q24) translocation specifically associated with leiomyoma. Other rearrangements affecting 12q14~q15, such as paracentric inversions, have also been reported. The rearrangements involving the same 12q region in leiomyoma and other benign solid tumors (e.g., angiomyxomas, breast fibroadenomas, endometrial polyps, hemangiopericytomas, lipomas, pulmonary chondroid hamartomas, and salivary gland adenomas) support the notion that critical genes are located within 12q14~q15 (16)

Apart from the involvement of chromosome 12 in t(12;14), trisomy 12 is not a rare cytogenetic alteration in leiomyomas. Leiomyomas with a normal karyotype can have cryptic 12q inversions. Although 12q15 is often part of t(12;14) in leiomyoma, and der(14)t(12;14)(q15;q23~q24) is observed in most leiomyomas, rearrangements of chromosomes 1, 5, 8, and 10 often accompany 12q15 [6].

Early studies reported a deletion of chromosome 7 from band q11.23 to q36. Although interstitial deletions and translocations involving chromosome 7q have also been observed in lipomas and endometrial polyps, the deletion is more commonly seen in myomas than in any other solid tumor. Previous reports of inversions and translocations involving 7q22 suggest that a region within this cytogenetic band is critical to the pathobiology of uterine leiomyoma (21). In addition, del may be associated with t(12;14) or t(1;6), suggesting the involvement of del(7) in the karyotypic evolution of leiomyoma[16].

Interstitial deletion of chromosome 7, del(7) (q22q32) is seen with an incidence of about 17% in karyotypically abnormal leiomyomas. Leiomyomas with deletions or translocations of chromosome 7 usually occur in a mosaic state with 46, XX cells. The apparent negative selection of these aberrant cells in tissue culture results in frequent loss of del(7)(q22q32) cells. Cells with del(7)(q22q32) are more likely to persist in cultures when t(12;14) is also present [2].

The instability of del(7)(q22q32) cells without aberrations of chromosome 12 is intriguing in light of the observation that myomas with abnormalities or rearrangements of chromosome 12 are often larger than tumors with abnormalities of chromosome 7, and larger myomas are more likely to be chromosomal abnormalities. than smaller ones. Observations of tumor instability in

culture and decreased tumor size in association with del(7) (q22q32) suggest that the gene regulating cell growth may reside in 7q22. Dissecting 7q22 to study leiomyoma-specific sequences is complicated by the fact that it is a densely gene-dense region that includes genes involved in developmental processes (DLX5, DLX6) and collagen metabolism (collagen type 1, procollagen-C-endopeptidase enhancer) as well as those encoding acetylcholinesterase, plasminogen activator inhibitor type 1, and mucin [21].

The occurrence of deletions in both chromosome homologs in the same region strongly suggests the involvement of a tumor suppressor gene in the development or progression of uterine leiomyoma [16].

6p21 rearrangements have been observed in benign mesenchymal tumors including lipomas, pulmonary chondroid hamartomas, endometrial polyps, and leiomyomas. In leiomyomas, these rearrangements occur at a frequency of 5% and include t(1;6)(q23;p21), t(6;14)(p21;q24), and t(6;10) (p21;q22). and inversions and translocations with other chromosomes [1].

Other cytogenetic abnormalities have been reported in leiomyomas and are less common than those mentioned above. These include X-chromosome alterations, including del(X)(p11.2), t(X;12)(p22.3;q15), -X, der(5)t(X;5)(p11;p15), del(X)(q12), der(X)t(X;3) (p22.3;q11.2), and inv(X)(p22q13). Although either the short or long arm of the X chromosome is rearranged, the Xp11~p22 region may be predominantly involved. Structural rearrangements of chromosome 1 in leiomyoma, especially in the form of ring chromosomes, usually occur simultaneously with other chromosomal changes and are therefore considered secondary abnormalities. Other structural aberrations of chromosome 1 found in leiomyoma include t(1;6)(q23;p21) and t(1;2)(p36;p24). Monosomy 10 and 10q deletions (especially the q22 band) were found in leiomyoma. A number of rearrangements of chromosome 3 were observed in leiomyoma, both as isolated abnormalities and as concomitant with other rearrangements, including: ins(2;3)(q31;p12p25), del(3)(p14), del(3) (q24). and t(3;7)(p11;p11). A subgroup of leiomyomas with 13q aberrations has been described, with deletions in this arm possibly playing a major role in development. [12, 16].

Conclusion: Uterine myoma is the most common benign tumor of the female genital tract, and the etiology of leiomyomas is still unknown. Cytogenetic abnormalities indicate different genetic pathways for myoma growth and development. Although most uterine leiomyomas have a normal karyotype, reports indicate that 50% of these tumors carry specific chromosomal aberrations that include chromosomes 3, 6, 7, 13, trisomy 12, reciprocal translocation between chromosomes 12 and 14, and monosomy 22. Such chromosomal rearrangements may be responsible for the occurrence as well as growth of these tumors.

The cytogenetic abnormalities identified to date demonstrate the genetic heterogeneity of these tumors. Further molecular analysis will help identify putative candidate genes in uterine leiomyoma formation. Identification of the genes involved may help in genetic diagnosis of the disease, prediction of genetic risks and treatment of the disease with appropriate therapeutic measures

REFERENCES

1. Katorkina E. S., Shatunova E. P. Modern aspects of etiology and pathogenesis of uterine myoma / Science and Innovations in Medicine. - 2017. - №. 1. - P . 6-12.
2. Ukhanova Yu Yu. MARKERS OF PROLIFERATION AND APOPTOSIS IN DIAGNOSTICS OF PROLIFERING Uterine Myoma // Editorial Board. - 2017. - P. 192.

3. Арипова, Ф., Таджиева, М., Назарова, К., & Закирходжаева, Д. (2015). Структура и частота гинекологических заболеваний среди девочек и девушек в некоторых регионах узбекистана. *Журнал вестник врача*, *1*(3), 7-9.
4. Арипова, Ф. С., Ищенко, И. В., Назарова, К. Я., & Мухамедханова, Ш. Т. КОМПЛЕКСНОЕ ОБСЛЕДОВАНИЕ, ДИАГНОСТИКА, ЛЕЧЕНИЕ И ПРОФИЛАКТИКА ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ ОРГАНОВ РЕПРОДУКТИВНОЙ СИСТЕМЫ У ДЕВОЧЕК. *МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ УЗБЕКИСТАН РЕСПУБЛИКАНСКИЙ СПЕЦИАЛИЗИРОВАННЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ МЕДИЦИНСКИЙ ЦЕНТР АКУШЕРСТВА И ГИНЕКОЛОГИИ АССОЦИАЦИЯ ВРАЧЕЙ ЧАСТНОЙ ПРАКТИКИ УЗБЕКИСТАНА КЛИНИКА «MAHLIYO-SHIFO» & V «MAHLIYO-SHIFO» & V*, 15.
5. Юлдашева, С. З., & Тиллашайхова, М. Х. (2017). Интеграция пищеварительно-всасывательной и иммунной функции в слизистой оболочке тонкой кишки и регуляция гомеостаза. *European journal of biomedical and life sciences*, (2), 3-7.
6. Юлдашев, А. Ю., Юлдашева, С. З., Рахматова, М. Х., Нишанова, А. А., & Таринова, М. В. (2014). Морфологические особености формирования слизистой оболочки фундального отдела желудка крыс в постнатальном онтогенезе. *Мир медицины и биологии*, *10*(4-2 (47)), 214-219.
7. Юлдашев, А. Ю., Юлдашева, С. З., Рахматова, М. Х., Нишанова, А. А., & Таринова, М. В. Ташкентская медицинская академия, Ташкентский педиатрический институт, г. *Ташкент МОРФОЛОГИЧЕСКИЕ ОСОБЕНОСТИ ФОРМИРОВАНИЯ СЛИЗИСТОЙ ОБОЛОЧКИ ФУНДАЛЬНОГО ОТДЕЛА ЖЕЛУДКА КРЫС В ПОСТНАТАЛЬНОМ ОНТОГЕНЕЗЕ*.
8. КУРБАНОВ, А., & КУЧКАРОВ, А. (2019). ИССЛЕДОВАНИЯ В ОБЛАСТИ ЭТНИЧЕСКОЙ ДЕРМАТОГЛИФИКИ. *ББК 60 С 56*, 188.
9. Курбанов, А. Т., Кучкаров, А., Камилжанова, Л., & Хусанова, Ш. (2018). ИЗУЧЕНИЕ МОРФОЛОГИИ КОЖНОГО РЕЛЬЕФА. *Мировая наука*, (11 (20)), 165-168.
10. Курбанов, А. Т., & Низомхожаева, Ш. Б. (2016). АСПЕКТЫ ДЕРМАТОГЛИФИКИ ЛАДОНИ ПО ПОЛОВОЙ ПРИНАДЛЕЖНОСТИ. In *Теоретические и практические проблемы развития современной науки* (pp. 121-122).
11. Искандаров, А. И., Садыкова, Н. Д., & Сирота, А. Р. (1989). Состояние некоторых показателей иммунологического статуса экспериментальных животных при остром отравлении пестицидами. *Доклады АН УзССР*, (11), 59.
12. Пулатова, Л. Т., & Искандаров, А. И. (2022). Современные возможности экспертных иследований в отношении наркотических средств, прекурсоров и их структурных аналогов. *The Scientific Heritage*, (104), 88-94.
13. Пулатова, Л. Т., & Искандаров, А. И. (2022). Роль экспертных исследований при идентификации и анализе синтетических каннабиноидов спайсов в изъятых материалах. *The Scientific Heritage*, (104), 94-99.
14. Кузиев, О. Ж., Рузиев, Ш. И., & Искандаров, А. И. (2014). Усовершенствование бескрасочного метода снятия отпечатков пальцев и ладоней. *Морфология*, *145*(3), 107-108.

15. Кузиев, О. Ж., Муродов, Н. Х., Мавлонов, У. О., & Отакулов, С. И. (2016). Особенности повреждений таза и нижних конечностей у водителей при несмертельной травме. *Молодой ученый*, (10), 512-514.
16. Ernazarova, F. R., Dzhumaev, K. C., & Kuziev, O. J. (2021). PROGRESS OF PREGNANCY IN WOMEN WITH CONFIRMED COVID-19. *EDITOR COORDINATOR*, *3*, 354.
17. Шамсиев, А. Я., Рузиев, Ш. И., & Курбанов, А. Т. (2016). Посмертное диагностирование сахарного диабета в судебной медицине. *Молодой ученый*, (11), 1186-1188.
18. Кузиев, О. Ж., Искандаров, А. И., & Рузиев, Ш. И. (2014). Значение программы IK в судебно-медицинской дерматоглифике. *Морфология*, *145*(3), 107-107a.
19. Кузиев, О. Ж., Рузиев, Ш. И., & Искандаров, А. И. (2014). Усовершенствование бескрасочного метода снятия отпечатков пальцев и ладоней. *Морфология*, *145*(3), 107-108.
20. Юнусова, Ш. Э., Насиров, Т. К., Жуманиёзов, Э. Х., & Пириева, Л. В. (2023). БАКТЕРИОЛОГИЧЕСКИЙ МЕТОД ОЦЕНКИ ПРИЖИЗНЕННОСТИ УТОПЛЕНИЯ.