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MORPHOLOGICAL CHARACTERISTICS OF UTERINE LEIOMYOMAS

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Abstract: This study examines the pathological and morphological characteristics of uterine leiomyomas based on the morphological analysis of materials obtained from 78 patients who underwent surgical treatment for uterine fibroids at the Gynecology Department of the Central Military Clinical Hospital of the Ministry of Defense. A total of 78 uterine leiomyomas were examined during the pathological examination. According to the anatomical localization of the examined myomas, submucosal, intramural and subserosal uterine leiomyomas were identified. Intramural myomas were found in most cases (55%), the least number of cases were recorded in the submucosal type. Histologically, the simple proliferative type was observed in 67% of cases, while the atypical type was the least common, occurring in 7.6% of cases. The high number of cells in the cellular type also led to the idea of a malignant tumor, but tumor necrosis and cell atypia, as well as pathological mitoses, were almost absent in cellular leiomyomas.

Keywords: myoma, leiomyoma, proliferation, uterus, subserosal, submucosal, intramural, myxomatosis, epithelioid.

Аннотация: Тадқиқотда Мудофаа вазирлиги Марказий ҳарбий клиник гопитали гинекология бўлимида бачадон миомаси туфайли жарроҳлик йўли билан даволанган 78 нафар беморлардан олинган материаллар морфологик текширув ўтказиш асосида бачадон лейомиомаларининг патоморфологик хусусиятларини ўрганиш саналади.

Патоморфологик текширувда 78 та бачадон леёмиомаси текширилди. Текширилган миомалар анатомик локализацияси бўйича субмукоз, интрамурал ва субсероз бачадон лейомиомалари аниқланди. Интрамурал миомалар кўп ҳолатларда учраб (55%), энг кам ҳолат субмукоз ҳолатда қайд қилинди. Гистологик жиҳатдан оддий пролиферацияланган тури 67% ҳолатда бўлса, атипик тури эса энг кам 7.6% ҳолатда аниқланди. Ҳужайрали турида ҳужайраларнинг кўплиги хавли ўсма тўғрисида ҳам фикр юритишга олиб келди, аммо ҳужайрали лейомиомаларда ўсма некрози ва ҳужайралар атипияси ҳамда патологик митозлар деярли учрамади.

Калит сўзлар: миома, лейомиома, пролиферация, бачадон, субсероз, субмукоз, интрамурал, миксоматоз, эпителиоид.

Аннотация: Целью исследования было изучение патоморфологической характеристики лейомиом матки на основе морфологического исследования материалов, полученных от 78 пациенток, перенесших хирургическое лечение по поводу миомы матки в гинекологическом отделении Центрального Военного Клинического госпиталя Министерства обороны. Патоморфологическое исследование включало 78 лейомиом матки. На основании анатомической локализации обследованных миом были выделены субмукозные, интрамуральные и субсерозные лейомиомы матки. В большинстве случаев (55%) были обнаружены интрамуральные фибромиомы, самая низкая частота зафиксирована в субмукозных случаях. Гистологически простой пролиферативный тип был выявлен в 67% случаев, тогда как атипичный тип был выявлен не менее чем в 7,6% случаев. Большое количество клеток в клеточном типе также наводило на мысль о доброкачественной опухоли, однако некроз опухоли и клеточная атипия, а также патологические митозы в клеточных лейомиомах практически отсутствовали.

Ключевые слова: миома, лейомиома, пролиферация, матка, субсерозный, субмукозный, интрамуральный, миксоматоз, эпителиоидный.

Introduction. Uterine fibroids (leiomyoma, fibromyoma) are benign monoclonal tumors originating from smooth muscle cells (myocytes) of the myometrium and are one of

the most common benign tumors of the female reproductive system in the world. Uterine fibroids are the most common benign monoclonal hormone-sensitive neoplasms of the uterus consisting of phenotypically altered smooth muscle myometrial cells, and are the second most common gynecological malignancy after pelvic inflammatory disease. Their incidence ranges from 20-77%, with an incidence of 3.3-7.8% in women under 30 years of age. The incidence of uterine fibroids varies with age, heredity, race, and body mass index [1, 3, 9].

According to foreign literature sources, 25-50% of fibroid nodes are associated with the location, size and number of them, the presence or absence of degenerative disorders. 40-50% of women with fibroids of reproductive age experience bleeding complications between menstrual cycles. In America, more than 600,000 hysterectomies are performed annually, of which more than 200,000 are related to uterine fibroids. 50-70% of uterine fibroids of reproductive age are performed with organ-preserving surgical operations. Currently, scientists are conducting research on the factors that trigger tumor transformation in smooth muscle cells and molecular mechanisms in the formation of uterine fibroids and are widely studied [7, 8, 11]. Leiomyomas can be single or multiple nodular formations, typically having a spherical shape, with a dense and hard consistency. On cross-section, they have a layered structure, the surface and the middle of which are of different colors, most often a whitish-gray color. The myomatous node is easily distinguished when separated from the surrounding myometrial tissue, slightly protruding [14]. Depending on the location of the myomatous nodes, the types of uterine leiomyomas are: submucosal-submucosal leiomyoma, intramural leiomyoma-interstitial, intermuscular leiomyoma, subserosal-external serous leiomyoma, interligamentous leiomyoma, cervical leiomyoma, and parasitic leiomyoma [2, 8, 12].

Among them, intramural leiomyomas of the uterine fundus and body are the most common in 95% of cases, while submucosal leiomyomas are the least common. As the nodes grow, they deform the endometrium, protrude into the cavity, causing bleeding. Sometimes, they are characterized by the development of pedicles that hold the nodes and penetrate the cervix, sometimes into the vagina. In some cases, leiomyomas can undergo cystic degeneration or calcification. In rare cases, leiomyomas have the property of adhering to other organs of the small pelvis, such cases are considered parasitic leiomyomas. They are formed as a result of the growth of smooth muscle cells and connective tissue fibroblasts in the myometrium [1, 3, 5]. There are several risk factors for the development of uterine fibroids, including age over 40, early menopause, infertility, late pregnancy, obesity, polycystic

ovary syndrome, hormone replacement therapy, black race, and a family history of uterine fibroids. These factors are strongly associated with an increased risk of developing uterine fibroids. There is now evidence that uterine fibroids are related to hormones, which are closely related to ovarian sex hormones [6, 7, 8].

The initial formation of uterine fibroid tumors involves somatic gene mutations, activation of estrogen, progesterone and their receptors, signaling pathways and enzymes, as well as complex interactions between numerous growth factors, forming a huge genetic susceptibility, gene mutations and hormonal control system. Further studies of the causes and pathogenesis of uterine fibroids from the perspective of gene mutations, activation of hormone receptors, etc. may lead to more accurate results. According to the genetic theory, the occurrence of uterine fibroids is associated with certain genetic diseases, and 40-50% of patients with uterine fibroids have an abnormal structure of chromosomes. In addition, molecular genetic studies have shown that enzyme disruption, cell apoptosis and a group of highly mobile proteins are associated with the pathogenesis of uterine fibroids. According to the sex hormone theory, uterine fibroids are most common in women of reproductive age with high sex hormone secretion, are very rare until puberty, and stop developing after menopause. During pregnancy, the production of estrogen and progesterone hormones increases, which creates conditions for the growth of fibroids. Treatment with drugs that reduce the secretion of sex hormones has been shown to reduce the development of fibroids. However, the role and mechanism of action of estrogen and progesterone in the pathogenesis of uterine fibroids have not been fully elucidated, and the question of whether they are the initial factors in the development of uterine fibroids remains controversial. According to the theory of primary stem cell mutation, molecular biological studies show that uterine fibroids are formed as a result of the proliferation of monoclonal smooth muscle cells, and that different cells in one fibroid originate from a single stem cell, which allows us to speculate that a single stem cell may have the properties of a stem cell, and this means that fibroids may arise as a result of a mutation in a single stem cell [5, 13, 14]. In addition, if the instability of smooth muscle cells during the long-term embryonic period leads to the appearance of cellular defects during the ontogenetic development of the uterus, another theory suggests that mature cells in the uterus are damaged and myoma develops from a progenitor cell. According to this theory, during each ovulation cycle, receptors for progesterone and various growth factors (TGF-β, EGF, bFGF) accumulate on

the surface of myometrial cells. During menstruation, under the influence of progesterone, the myometrium hyperplasias, progesterone binds to its specific receptors and indirectly leads to a uniform hyperplasia of the myometrium due to heterotopic expression of various growth factors. While type A receptors block the proliferation of myometrial cells, type B effector receptors cause the proliferative effect of progesterone. This dominance is most often observed in the peripheral area of the uterine muscle fibers with a good blood supply or in the developing myoma node. During the menstrual cycle without pregnancy and against the background of a decrease in progesterone levels, the apoptosis process of overly proliferating smooth muscle cells exposed to damaging factors through type A receptors is activated (spasm of the spiral arteries during menstruation, inflammatory processes, including traumatic effects due to medical interventions inside the uterus, the presence of endometriotic heterotopies). In this case, as a result of repeated proliferation during the menstrual cycle, an excess of type B receptors is formed on the surface of hyperplastic myometrial cells. With each menstrual cycle, the number of damaged cells accumulates, gradually leading to the formation of myomatous nodules with different growth potential. In the initial stages of growth, the active nodule develops due to physiological changes in hormones during the menstrual cycle. Estrogens stimulate the accumulation of progesterone receptors and epidermal growth factor, progesterone increases the expression of EGF, which stimulates proliferation and further growth of the myomatous nodule [11]. Morphology and classification of fibroids: Myomas can grow in any part of the uterus and are mainly composed of proliferating cells of uterine smooth muscle and a small amount of fibrous connective tissue. Myomas are usually spherical or irregularly shaped, have a solid structure, have well-defined boundaries, but are composed of compressed muscle fibers without a clear capsule. Myomas are mainly solid spherical tumors. On the cross-section, the tumor tissue is often light gray, twisted. If the fibroid grows rapidly or does not have an adequate blood supply, various secondary changes are observed, such as hyaline degeneration, mucinous-cystic changes, edema, hemorrhage, necrosis. The hardness and softness of uterine fibroids vary at different stages of their growth. Small fibroids and newly formed fibroids have a relatively soft structure, while large fibroids and old fibroids have a harder structure. The softness or hardness of fibroids is relative. The more fibrous components in the fibroid, the more colorless the tumor is and the harder its consistency. Uterine fibroids vary in size and can be single or multiple. Uterine fibroids are

divided into subserosal, submucosal, and intramural types depending on their location relative to the uterine wall. Intramural fibroids are fibroids located within the myometrium. All fibroids arise from the myometrium, therefore they are the most common, accounting for 60-70% of the total number (Fig. 3).

Subserosal fibroids are intramural fibroids that are located close to the serous layer of the uterus and are pushed out onto the uterine surface due to contraction of the uterine myometrium. The surface of the fibroid is covered only by the serous layer (Figure 4). If the tumor continues to grow in the direction of the serous surface and only one pedicle is attached to the muscular wall of the uterus, it is considered a pedicle subserosal fibroid, which is supplied by blood vessels. If the fibroid is located on the lateral wall of the uterine body, grows towards the uterus, and protrudes between the two sheets of the ligamentum flavum, it is called an intramural fibroid. This is a rare disease, accounting for approximately 2% [7, 9]. Submucosal fibroids are fibroids that grow below the mucosa and protrude into the uterine cavity, and are covered only by the mucosa. Most of them are called solitary and submucosal fibroids (Fig. 5). Most submucosal fibroids are located in the uterine cavity, mainly in its fundus, anterior and posterior walls, as well as on its side walls. Some of them are located in the area close to the inner surface of the cervical canal or cervix. Most intrauterine fibroids show that part of the tumor grows between the muscle walls, and part protrudes into the uterine cavity, and are called submucosal fibroids. Some fibroids also protrude completely into the uterine cavity and have a pedicle, such a myoma is called a pedicle-like submucosal fibroid [2, 7, 13].

In 2011, the International Society of Obstetricians and Gynecologists proposed the following classification of uterine fibroids, where fibroids are classified into types 0 to 8, with type 0 being on a thin stalk, type I having up to 50% of the node in the myometrium, and type II having more than 50% of the submucosal fibroids in the myometrium. Intramural fibroids: Type III is 100% intramural, with the outer edge of the tumor being 5 mm or more from the serous membrane of the uterus and in contact with the endometrium. Type IV is 100% intramural, with the outer edge of the fibroid being less than 5 mm from the serous membrane of the uterus. Subserosal fibroids: Type V is a fibroid located on the surface of the uterus, with more than 50% of the myometrium. Type VI fibroids are located subserosally and up to 50% of the node is located intramural. Type VII is a pedunculated subserosal fibroid. Type VIII includes other types of nodes, such as cervical, metastatic, and others.

According to the International Classification of Diseases-10 (ICD-10), the histological classification of fibroids is as follows: simple, cellular, active mitotic, lipoleiomyoma, epithelioid, bizarre, myxoid, vascular, hemorrhagic, myoma with hematopoietic elements.

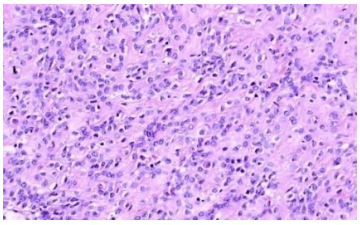

Figure 1. Epithelioid leiomyoma

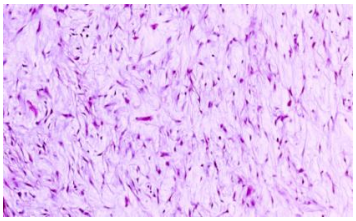

Figure 2. Myxoid myoma

Myxoid leiomyoma is a benign, thin-walled, smooth muscle tumor with abundant amorphous myxomatous inclusions among the tumor cells. The tumor boundaries are well-defined and there is no cellular atypia or mitoses.

Lipoleiomyoma is a typical leiomyoma characterized by the presence of numerous adipocytes scattered throughout the body. In addition to these types, active mitotic and hemorrhagic cell leiomyomas are also found. The active mitotic type is most common in premenopausal women, with up to 15 mitotic figures in 10 fields of view. However, this diagnosis is not made in cases of severe nuclear atypia, pathological mitosis, and coagulation necrosis.

Hemorrhagic leiomyoma (apoplectic) is a form of leiomyoma, which occurs mainly in pregnant or postpartum women taking oral contraceptives. Macroscopically, stellate hemorrhagic foci are visible, but coagulative necrosis of tumor cells is not observed. Physiological mitoses are detected, and the areas of hemorrhage are usually limited by a small zone of granulation tissue. According to the morphogenetic classification: 1. Simple myoma - benign hyperplasia of muscle tissue, mitoses are not detected (Fig. 9). 2. Proliferated myoma - tumor cells retain their normal structure, but mitoses in the cells do not exceed 25%. 3. Multiple focal proliferation of pre-sarcoma myogenic cells, with atypia, mitoses are found in up to 75%.

Research objective: Pathohistological study of uterine leiomyomas according to their anatomical location.

Research materials and methods: The study analyzed the results of pathohistological examination of uterine fibroids from 78 women who underwent surgery with a clinical diagnosis of "uterine fibroids" at the Gynecology Department of the Central Military Clinical Hospital of the Ministry of Defense in 2019-2024. After macroscopic examination of the uterine fibroids obtained in the study, sections were taken for histological examination. Hematoxylin-eosin stain preparations were prepared and examined microscopically (Figures 5, 7-9).

Results of the study and their discussion. The materials obtained in the study were examined in patients with uterine fibroids aged 30 to 60 years who applied to the National Center for Obstetrics and Gynecology during 2019-2024. It was found that the size of hyperplastic smooth muscle nodules ranged from a few millimeters to 10 cm. According to age groups, the highest rate was found in the age group of 40-60 years.

The number of patients in different age groups is presented in Figure3.

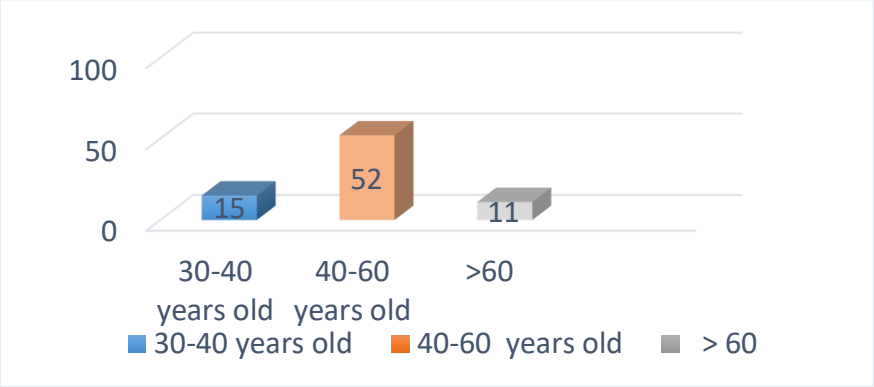

Figure 3. Distribution of 78 subjects with uterine fibroids by age group

When analyzing the location of uterine fibroids, the most common indicator was intramural fibroids (55%), followed by submucosal and subserous fibroids (36% and 9%, respectively).

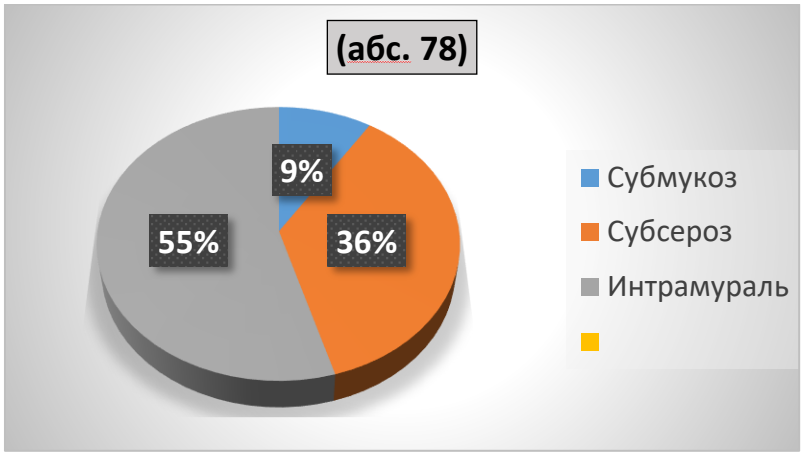

Figure 4. Percentages by localization of uterine fibroids

Figure 5. Myomatous nodes located in different anatomical areas

In myomatous nodes, the structure of the fibromyomatous structure, formed mostly from smooth muscle cells, is visible in the optical field, in all sections the myocytes are arranged chaotically, intertwined with each other in all directions and in all directions, the characteristic of coherence is preserved in all sections. The nuclei of the myocytes are oval, hyperchromic, sometimes fragmented, rich in chromatin, the cytoplasm is granular and eosinophilic. In the interstitial tissue, the growth of fibromatous foci is detected, the cells are spindle-shaped, fibrocytes, fibroblasts and histiocytes, the blood vessels are unevenly located, sometimes the walls are slightly thickened, due to fibrosis, the space is unevenly filled, sometimes in the perivascular areas focal fibromatous areas are visible. In some sections, cells consisting mainly of “myocyte-cell” clusters are visible in the deep layer areas, smooth muscle myocytes have also grown around the vessels and are subject to uneven proliferation /hyperplasia/, myocytes are sometimes polymorphic in appearance. Sometimes among the myocyte cells, there are focal and sporadically enlarged and sharply hyperchromic, oval and polygonal mononuclear and binuclear cells, with a small number of mitoses. In all sections, the consistency and irregular complexity are almost preserved, smooth muscle cells

/myocytes/ are monomorphic, sometimes straight mitoses are visible in the nuclei of myocytes. In rare cases, **leiomyoma manifests** itself in the form of nuclear pleomorphism, but no mitotic figures or necrosis of tumor cells are observed.

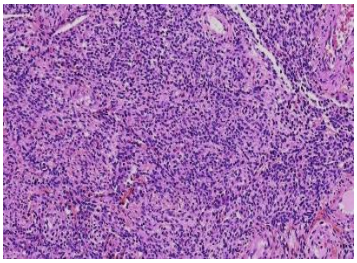

Figure 7. "Cellular" leiomyoma. Stained with hematite and eosin, magnified 10x20 times..

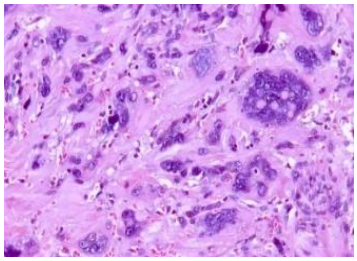

Figure 8. Atypical (strange) leiomyoma. Stained with hematoxylin and eosin, magnified 10x20 times.

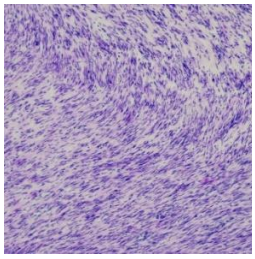

Figure 8. Atypical (strange) leiomyoma. Stained with hematoxylin and eosin, magnified 10x20 times.

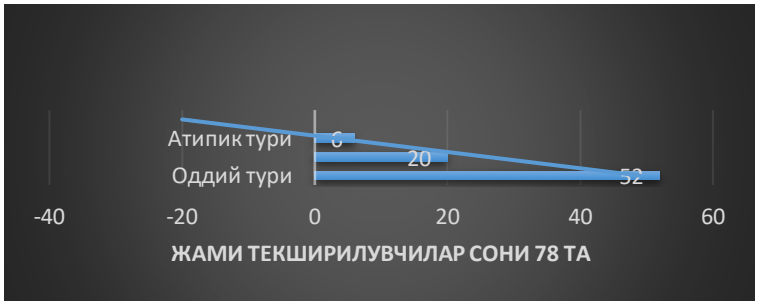

Figure 6. Morphogenetic occurrence of uterine fibroids

During the studies, cellular leiomyoma was detected in less than 6% of leiomyomas, and the number of cells in it was significantly higher than the surrounding myometrial cells. In some cases, the abundance of cells also suggests the possibility of a benign tumor, but tumor necrosis and cell atypia, as well as pathological mitoses, were almost absent in cellular leiomyomas (Fig. 7-9).

Morphological and histological variants of uterine leiomyoma are diverse, each of which has its own characteristics. If earlier, the treatment of fibroids was aimed at reducing the proliferation of smooth muscle cells, then later it was proven that in such cases it is necessary to take into account all its morphological features, including the connective tissue

between them. Therefore, in the treatment of uterine fibroids, their anatomical, histological and morphogenetic characteristics should be taken into account.

CONCLUSION

In the analysis of uterine fibroids by age, the highest rate was found in the age group of 40-60 years, while in the analysis by location, the highest rate was found in intramural fibroids (55%). Histologically, the simple proliferative type was detected in 67% of cases, and the atypical type was detected in at least 7.6%. In the cellular type, the abundance of cells also suggests a malignant tumor, but tumor necrosis and cell atypia, as well as pathological mitoses, were almost absent in cellular leiomyomas.

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