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Morphological features and the functional state of connective tissue of the uterine rudiments in reproductive age patients with Mayer–Rokitansky–Küster–Hauser syndrome

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Introduction. Female patients with Mayer–Rokitansky–Küster–Hauser syndrome (MRKH) have high stigma scores; the condition severely affects the reproductive system. The study aimed at specification of morphological features and assessment of the maturity of connective tissues of the uterine rudiments in MRKH.

Patients and methods. The study included 42 patients with vaginal and uterine aplasia having functioning uterine rudiments and 47 patients of the control group without genital malformations. Age of the patients was 20-24 years in 67.2% of the cases, and 31.2% of the patients were aged ≤ 19, inclusive. Immunohistochemical assay was applied to determine expression levels of collagen I, collagen III, MMP2, MMP9, TIMP1, fibronectin and laminin proteins within the functioning uterine rudiments in comparison with levels of the same proteins in normally developed uterine tissues.

Results. Decreased expression of collagen type I and elevated levels of MMP2 and MMP9 proteins in uterine tissues were observed for the group of patients with MRKH.

Conclusions. 1) Uterine rudiments in patients with MRKH show variable degree of morphological similarity with the normally developed uterus; 2) The functioning uterine rudiments are subject to the same pathological processes as the normally developed uterus (myoma, endometriosis). 3) The functioning uterine rudiments in patients with MRKH show altered patterns of connective tissue remodeling, with decreased expression of collagen type I and increased expression of matrix metalloproteinases MMP2 and MMP9.

Keywords: Müllerian aplasia, uterine rudiments, metalloproteinases, connective tissue remodeling, MMP2, MMP9

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Морфологические особенности и состояние соединительной ткани маточных рудиментов пациенток репродуктивного возраста с синдромом Мейера–Рокитанского–Кюстера–Хаузера

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Введение. Пациентки с синдромом Мейера–Рокитанского–Кюстера–Хаузера (МРКХ) имеют высокий порог стигматизации и находятся в зоне риска развития заболеваний женской репродуктивной

системы. Цель исследования – выявить морфологические особенности и оценить зрелость соединительнотканных структур маточных рудиментов при синдроме МРКХ.
Материалы и методы. Обследованы 42 пациентки основной группы с аплазией влагалища и матки с функционирующими рудиментами и 47 пациенток группы контроля без пороков развития половых органов, средний возраст которых в 67,2% случаев приходился на возрастную группу 20–24 года, в 31,2% случаев – на группу до 19 лет включительно. Проведены иммуногистохимические исследования функционирующих рудиментов матки для выявления уровня экспрессии белков коллагена I, коллагена III, MMP2, MMP9, TIMP-1, фибронектина, ламинина.
Результаты. Выявлено снижение уровня экспрессии коллагена I и повышение уровня экспрессии MMP2 и MMP9 в основной группе пациенток с функционирующим маточным рудиментом.
Заключение. 1) Строение маточных рудиментов у пациенток с синдромом МРКХ может быть приближено к строению тела матки с функционирующим эндометрием, а может существенно отличаться. 2) Функционирующие рудименты матки могут подвергаться тем же патологическим процессам, что и нормальная матка (миома, эндометриоз). 3) В функционирующих маточных рудиментах при синдроме МРКХ по сравнению с группой контроля выявлены признаки замедления процессов ремоделирования соединительной ткани: снижение уровня зрелого коллагена I и повышенный уровень экспрессии матриксных металлопротеиназ MMP2 и MMP9.

Ключевые слова: аплазия влагалища и матки, маточные рудименты, металлопротеиназы, ремоделирование, MMP2, MMP9

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Introduction

Congenital aplasia of the uterus is pathognomonic for the Mayer-Rokitansky-Küster-Hauser syndrome (MRKH, a.k.a. Müller's aplasia) and testicular feminization syndrome (a.k.a. androgen insensitivity syndrome) [1–3]. Such defects can also be observed in combined malformations of the urinary system and gastrointestinal tract (cloacal malformations and anorectal anomalies) [4] and some other syndromic malformations, e.g. oculo-auriculo-vertebral syndrome, Al-Awadi/Raas-Rothschild syndrome, Klippel-Feil anomalies, etc. [5, 6].

Patients with MRKH have normal female karyotypes and normally functioning ovaries, which ensure proper development of gender-specific traits. Still, the patients either lack the uterus and upper portion of the vagina, or have uterine rudiments. The syndrome occurs with a frequency of 1 in 5000 newborn girls. The etiology of MRKH development is still unknown and is considered by most authors within the framework of embryonic disorders [7–9].

MRKH typically presents with either complete aplasia of the uterus (64%) or the presence of functioning uterine rudiments (24%) and developmental abnormalities of the fallopian tubes and ovaries in combination with multiple malformations of other organs and systems [10, 11].

Despite the obvious genetic causation associated with increased stigmatization in the patients with genital defects, morphological and molecular mechanisms of MRKH onset remain unclear. Immunohistochemical (IHC) profiles of connective tissues in the uterine rudiments (content of different types of collagen, metalloproteinases (MMPs) and their inhibitors (TIMPs), fibronectin and laminin) require further investigation [12].

The aim of this study was to identify morphological features and assess the maturity of connective tissue of the functioning uterine rudiments in patients with MRKH.

Patients and methods

The study included 42 patients with karyotype 46XX, having vaginal and uterine aplasia with a functioning uterine rudiment, admitted to the Department of Operative Gynecology of the V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology for surgical correction of genital malformations during the period 1995-2016. These patients constituted the MRKH group. The control group consisted of 47 patients without

genital malformations admitted for surgical treatment of gynecological conditions during the same period. Age of the patients constituted 20-24 years in 67.2% of the cases, and 31.2% of the patients were aged ≤ 19, inclusive. All patients of the MRKH group complained about the absence of menstruation and the inability to have sex due to vaginal dysplasia. In 23 cases (54.8%), the patients with MRKH complained about cyclical pains in the lower abdomen. Nine patients (21.4%) of the MRKH group had natural colpopoiesis as a result of regular attempts at sexual activity.

The methods included anamnestic, physical, genetic (karyotyping) and ultrasound examination of the pelvic cavity and kidneys, complemented with MRI in certain cases to exclude other complex/syndromic malformations and/or excretory urography to assess functional state of the urinary system and the kidneys. Most of the patients were admitted to the V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology with indications for surgical correction (colpopoiesis).

Surgical specimens were collected from all patients for routine histological examination and immunohistochemical assessment of connective tissue markers.

For immunohistochemistry, 4 μm paraffin sections were slide-mounted and dried at +37 °C for 18 hours. Deparaffinized sections were rehydrated in ethanol series (95°, 80° and 70°, for 2 minutes each). The epitope retrieval was carried out in a PT Link station (Dako, USA) using 10 mM citrate buffer, pH 6.0, at 97 °C for 20 minutes. The cooled slides were placed in humid chambers (to prevent drying) and incubated for 15 minutes in a 3% hydrogen peroxide solution to block the endogenous peroxidase activity. The reaction with primary antibodies was carried out for 30 minutes at room temperature. The list of primary antibodies used in the study included monoclonal mouse antibodies to MMP2 (clone 6E3F8, 1:200, Abcam, UK) and monoclonal rabbit antibodies to MMP9 (clone EP1254, 1:200, Abcam, UK), as well as polyclonal rabbit antibodies to TIMP1 (1:50, NeoMarkers, USA), Fibronectin (1:50, Dako, Denmark), Laminin alpha-1 (1:50, Santa Cruz Biotechnology, USA), Collagen I alpha-1 (1:500, GeneTex, USA), and Collagen III alpha-1 (1:1000, GeneTex, USA).

Vizualization of the signals was accomplished with the use of Dako REAL EnVision Detection System (Peroxidase/DAB+, Rabbit/Mouse; Dako, Denmark) as secondary antibodies. The oxidation of the 3,3-diaminobenzidine (DAB) substrate by horseradish peroxidase in the presence of hydrogen peroxide yielded the water-insoluble brown final product. For correct interpretation of the IHC data, appropriate controls were included in each series, with negative controls set without the addition of primary antibodies and positive controls for each antibody selected according to the manufacturer's specifications. Following the IHC reactions, the sections were counterstained with Mayer's hematoxylin and embedded in Shandon™ synthetic mountant (Thermo Fisher Scientific, USA). Connective tissue structures were characterized based on the appearance of extracellular matrix and cellular elements. The maturity of connective tissue was assessed by expression levels of collagens, fibronectin and laminin, MMP2, MMP9 and TIMP1. The images were characterized by conventional semi-quantitative scoring, with grade 0 for the lack of positive signal, grade 1 for ≤ 20%, grade 2 for 20-40%, and grade 3 for ≥ 40% of reactive cells [13].

Results

The predominant type of surgical treatment was pelvic peritoneal colpopoiesis (71.4% of the cases, n = 30). Concomitant intraoperative findings included hypoplasia or aplasia of fallopian tubes, congenital unilateral absence of a fallopian tube and ovary (n = 2) and an elongated ovary with suspected ovotestis (n = 3).

Morphological examination of the rudimentary uterine bodies revealed functionally active focal endometrium in 17 (40.5%) of the cases, with 12 of them comprising proliferative phase and 5 specimens comprising secretory phase. Focal endometrium without signs of functional activity was observed in 9 cases (21.4%). In the rest 16 cases (38.1%), no endometrium was identified. Morphological examination of the rudimentary uterine horns revealed endometrium with the signs of functional activity (most often corresponding to proliferative phase) in 30 cases (71.4%, Fig. 1 B).

In addition, the examination revealed internal endometriosis in seven patients (16.7% of the cases) and thin endometrium with inflammatory changes in five patients (11.9% of the cases).

Control images represent myometrium and endometrium of the normally developed uterus (Fig. 1A); the material was obtained during laparoscopic management of common uterine pathologies, mostly fibroids. Figure 1B shows muscle tissue of a functioning rudimentary horn; the insert represents an area with lining endometrium.

IHC study of the resected material revealed expression of collagen type I within endometrial stroma in 37 patients of the MRKH group (88.1% of the cases) and 47 patients of the control group (100% of the cases). Ubiquitous expression of collagen type I in myometrium was observed in both groups (Fig. 1 C, D).

Ubiquitously high expression of collagen type III within endometrial stroma and myometrium was observed in both groups. By contrast, no expression of collagen type III in endometrial glands was detected in any of the specimens examined.

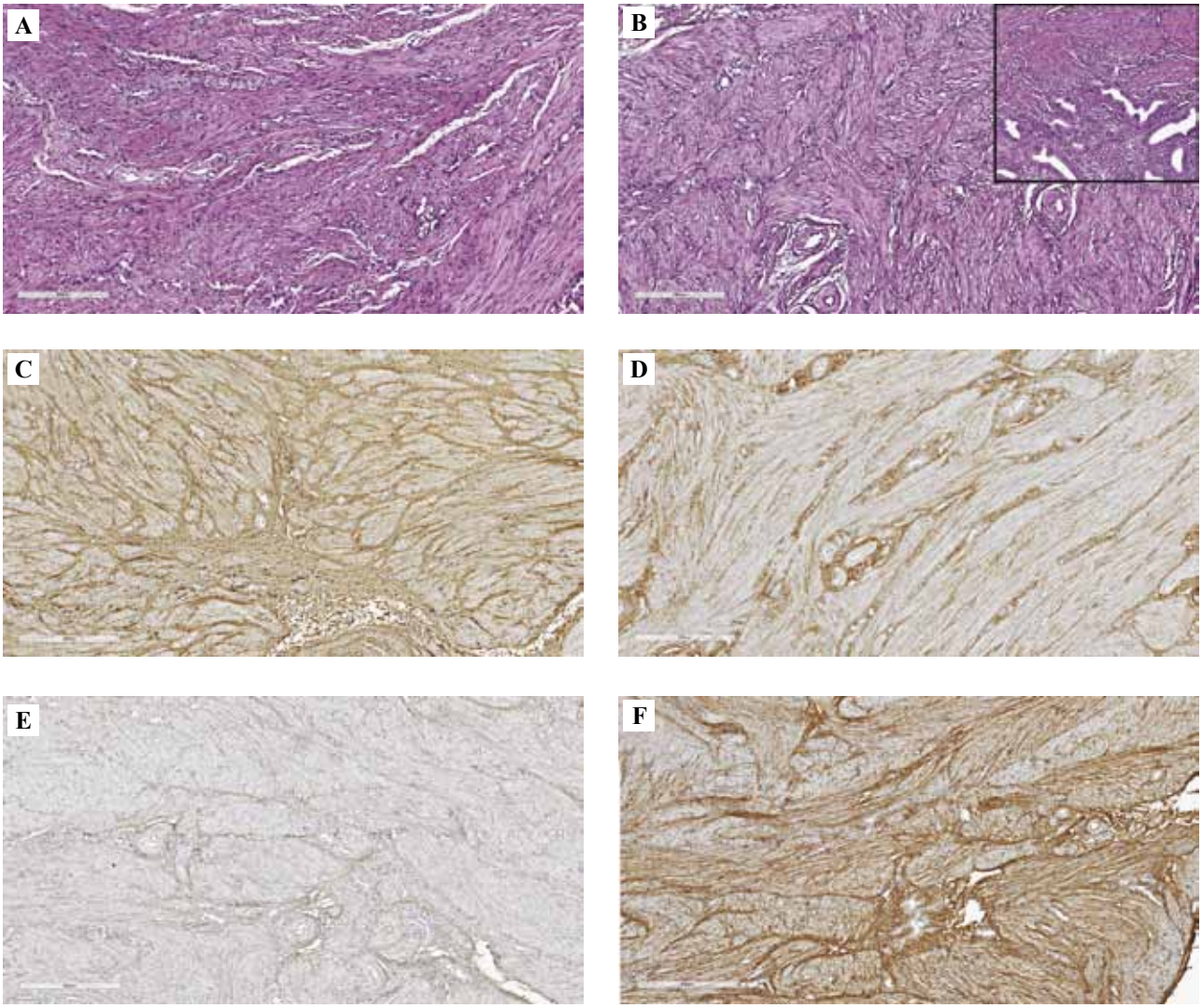

Fig. 1. Morphology and immunophenotype of myometrium in women without uterine malformations and patients with Mayer–Rokitansky–Küster–Hauser syndrome.
A – normal myometrium, B – myometrium of the functioning remnant horn (in the box: endometrium present), C – collagen I expression in normal myometrium, D – collagen I expression in myometrium of the functioning remnant hornmuscle tissue, E – MMP9 expression in normal myometrium, F – MMP9 expression in myometrium of the functioning remnant hornmuscle tissue. A, B – H&E stain, scale bar 200 μm, C–F – immunohistochemical assay, scale bar 300 μm

Рис. 1. Морфология и иммунофенотип неизмененного миометрия женщин без пороков развития матки и пациенток с синдромом Мейера–Рокитанского–Кюстера–Хаузера.
А – неизмененный миометрий, В – мышечная ткань функционирующего рудиментарного рога (во врезке – с наличием выстилающего эндометрия), С – экспрессия коллагена I типа в миометрии женщин контрольной группы, D – экспрессия коллагена I типа в мышечной ткани рудиментарного рога, E – экспрессия MMP9 в миометрии женщин контрольной группы, F – экспрессия MMP9 в мышечной ткани рудиментарного рога. A, B – окраска гематоксилином и эозином, масштабный отрезок 200 мкм, C–F – иммуногистохимическое окрашивание, масштабный отрезок 300 мкм

IHC staining for MMP2 (a.k.a. gelatinase A) revealed positive signals in the cytoplasm of endometrial gland cells in all patients of both groups. In the MRKH group, the MMP2 staining intensity was higher than in the control group. Within endometrial stroma, the MMP2 signal was observed in one patient of the MRKH group and none of the patients of the control group. Within myometrium, the MMP2 signal was observed in two patients of the MRKH group and one patient of the control group. The data indicate that (1) expression of MMP2 in the uterus is typically confined to endometrial glands and (2) MMP2 is stronger expressed in uterine rudiments than in normally developed uteruses.

IHC staining for MMP9 (a.k.a. gelatinase B) revealed its expression in endometrial glands in 16 patients of the MRKH group (38.1% of the cases). In endometrial stroma, the corresponding signal was observed in 32 patients of the MRKH group (76.2% of the cases), and its level was increased significantly compared with the control group (Fig. 1 E, F). In myometrium, the distinct MMP9 signal was observed for 26 patients of the MRKH group (61.9% of the cases) and none (0%) of the control group patients.

Thus, expression levels of MMP2 and MMP9 in uterine tissues were higher in the MRKH group compared with the control group. Expression levels of TIMP1, adhesive glycoprotein laminin and fibronectin were detectable in none (0%) of the tissue samples examined.

Discussion

Histological analysis of the uterine rudiments with confirmed functional activity revealed predominance of proliferative phase (observed in 71.4% of the cases), with secretory phase being less common. This observation is consistent with published evidence indicating that endometrium of the uterine rudiments consists mainly of the basal layer [14]. Certain studies suggest the possibility of proper endometrial differentiation in the uterine rudiments, while also noting that the differentiation is less pronounced in patients with concomitant malformations of other organs and systems [15]. The violation of decidualization processes in the endometrium of uterine rudiments compared with the endometrium of normally developed uteruses has been also confirmed histologically [16]. However, the reported findings on the endometrial cycle in MRKH are incidental, and no systemic efforts can be undertaken as yet due to the lack of uniform criteria for the morphological assessment.

The IHC data obtained by us in this study indicate decreased expression of collagen type I in the myometrium of functioning uterine rudiments compared with the myometrium of normally developed uteruses. A decrease in the levels of mature collagen may indicate decreased rates of connective tissue remodeling associated with abnormal synthesis/assembly of collagen, as well as its excessive degradation, impaired cross-linking, autoimmune reactivity, etc. As is known, collagen diseases not necessarily represent a consequence of mutations in the collagen-encoding genes *per se*, but may also result from defects in collagen biosynthesis, post-translational modification, secretion, remodeling and self-assembly; all these stages are served and orchestrated by a plethora of genes [17].

The results obtained in this study indicate increased expression of matrix metalloproteinases MMP2 and MMP9 in the functioning uterine rudiments of patients with MRKH. Metalloproteinases are involved in tissue remodeling, angiogenesis, cell growth, cell migration and differentiation, apoptosis, extracellular matrix turnover, etc. The increased MMP levels observed within the uterine rudiments may reflect the functional failure. It should be noted that, reportedly, these levels may vary, with MMP2 expression in certain cases hardly exceeding the lower detection limit [15].

The obtained results still prevent clear conclusions about the existence of characteristic patterns of distribution, expression and accumulation of metalloproteinases within the uterine rudiments. Further studies in this direction are needed to support and expand these primary IHC profiles of connective tissue structures of the uterine rudiments in MRKH.

Conclusions

Uterine rudiments in patients with MRKH show varying degree of morphological similarity with the normally developed uterus. The degree of alterations in functional morphology of the uterus (myometrial hypotrophy, endometrial insufficiency) correlates with concomitant malformations of other organs in these patients.

The functioning uterine rudiments in MRKH are subject to the same pathological processes as the normally developed uterus (fibroids, endometriosis).

Decreased rates of connective tissue remodeling were revealed in the group of patients with functioning uterine rudiments compared with the control group, including a decrease in the levels of mature collagen type I and increased expression levels of matrix metalloproteinases MMP2 and MMP9.

Author contributions

Conceived the study and designed the experiments – A.V. Asaturova, M.V. Bobkova, L.V. Adamyan.

Collected the data and performed the analysis – A.V. Asaturova, A.V. Tregubova, M.V. Bobkova, T.U. Smolnova, A.S. Arakelyan.

Carried out IHC reactions and analysed the results – N.M. Fayzullina, A.V. Asaturova, A.V. Tregubova.

Wrote the paper – A.V. Asaturova, M.V. Bobkova.

Edited the manuscript – A.V. Asaturova, N.M. Fayzullina, L.V. Adamyan., T.U. Smolnova.

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