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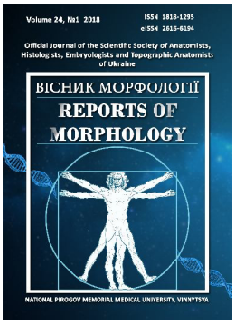

Expression of mmp-9 as a prognostic factor of uterine sarcoma

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Uterine sarcoma is a highly aggressive mesenchymal neoplasm with an extremely unfavorable prognosis. Up today there are still relevant issues concerning search for clinical-morphological and biomolecular criteria for prognosis relapse-free survival of uterine sarcoma patients. It is well-known, the increase of the expression level of MMP-9 in primary tumor or metastatic foci correlates with a low differentiation of tumor cells, high ability for invasiveness, high metastatic activity, and shortened life expectancy. It's still unknown, whether it is possible to consider the expression of MMP-9 in uterine sarcoma cells as a convincing prognostic factor. For many types of epithelial malignant neoplasms, high metastatic rate is associated with an increase level of MMP-9 both in plasma and in tumor tissue. The purpose of this study is to investigate the features of MMP-9 expression in uterine sarcoma cells for development of the model for individual prediction of the disease course. The study of the surgical material of selected 54 cases of uterine sarcoma of stage I-II (according to FIGO criteria) with a known prognosis of the disease, which were distributed depending on the morphological type done: leiomyosarcoma (LMS) - 18 cases, endometrial stromal sarcoma (ESS) - 22 cases, undifferentiated sarcoma (US) - 14 (according to the classification of tumors of the uterus of the WHO). For histological examination, pieces of tissue were cut from different parts of the tumor nodes - central, peripheral, parts of the adjacent intact tissue of myometrium (total of 6-8 bits). The tumor cell phenotype was determined using low molecular weight cytokeratins (Cytokeratin PAN, AE1/AE3), smooth muscle actin (Smooth Muscle Actin, 1A4), myogenin (Myogenin (F5D)), CD 10 and vimentin (Vimentin, V9). The histochemical label was evaluated in two parameters: the degree of prevalence and intensity of coloration. To assess the color intensity, a qualitative scale was used: 0 - no reaction, 1+ - weak cytoplasmic coloration to 30.0% of tumor cells, 2+ - moderate reaction, 30.0 to 60.0% of stained cells, 3+ - pronounced cytoplasmic reaction in 60.0-100.0% of tumor cells. Statistical processing of the data was performed using the "STATISTICA 10.0" program package. The conducted study has showed, the negative (0) and weak (1+) expression of matrix metalloproteinase-9 were observed in the most part of ESS and only partially in US. Despite the stage of the disease, with such a status of MMP-9, there was observed no signs of relapsed disease. The moderate (2+) and high (3+) expression of MMP-9 was detected in 44.5 % of uterine sarcoma, in the most part in LMS patients. However, if in LMS cases the progressive disease was observed only in one third of them (4 of 12 cases), in case of ESS and US, in all the patients with such tumors status there was observed relapsed disease. Such a reaction may be indicative for invasive and metastatic potential of ESS and US and cause of the hematogenous metastases.

Keywords: *uterine sarcoma, MMP-9 expression, connection of MMP-9 expression and tumor progression, leiomyosarcoma, endometrial stromal sarcoma, undifferentiated uterine sarcoma.*

Introduction

Uterine sarcoma is a highly aggressive mesenchymal neoplasm with an extremely unfavorable prognosis [24, 39]. The intraorganic location of tumor sites causes low accessibility and informative visual and instrumental research. In this regard, tumor data are still rarely found in the early stages of its development [25]. The share of sarcoma among all malignant neoplasms is only 3.0%, which is why these tumors are still one of the less well-known tumors of this localization [32, 34].

The issue of finding clinical and morphological and biomolecular prediction criteria and non-recurrent survival in tumors of the uterus is still topical. It has been established that during metastasis, tumor cells interact with the extracellular matrix (ECM), associated with it growth factors and cytokines, basal membranes, endothelial cells, circulating blood cells, and others [16]. The degradation of ECM occurs as a result of a violation of the regulation of all its components, which leads to tumor invasion [3, 20].

For many types of epithelial malignant neoplasms, high metastasis rates are associated with an increase in the level of matrix metalloproteinase-9 (MMP-9) in both plasma and tissue parenchyma.

A retrospective analysis of the studies in these patients suggests that elevation of MMP-9 expression in the primary tumor or metastases correlates with low differentiation of tumor cells, high carcinoma invasiveness, high metastatic activity, and shortening of life expectancy [22, 31].

It is still unknown whether it is possible to consider the expression of MMP-9 in uterine sarcoma cells as a convincing prognostic factor.

That is why *the purpose* of this research is to study the features of expression of MMP-9 in uterine sarcoma cells to create a model for individual prediction of the course of the disease.

Materials and methods

The study of the surgical material obtained during surgical treatment of patients in the department of oncogynecology State Institution "Grigoriev Institute for Medical Radiology of National Academy of Medical Sciences Ukraine" from 2010 to 2018, as well as fixed archival material and paraffin blocks of tissue that were obtained from patients operated at the Kherson Regional Oncology Center (on the basis of an agreement on scientific cooperation). We selected 54 cases of uterine sarcoma of stage I-II according to the FIGO criteria [23], with a known prognosis of the disease, which were distributed according to the classification of the tumors of the uterus of the WHO [29] depending on the morphological type: leiomyosarcoma (LMS) - 18 cases, endometrial stromal sarcoma (ESS) - 22 cases, undifferentiated sarcoma (US) - 14. In order to guarantee the quality of immunohistochemical studies, coded samples were processed simultaneously in the laboratories of KMAPE, Ukraine, and the University of Sweden, with subsequent decoding of the results by the leader of the research and data entry for analysis only if there is consensus in the conclusions of both laboratories.

For histological examination, pieces of tissue were cut from different parts of the tumor nodes - central, peripheral, parts of the adjacent intact tissue of myometrium (total of 6-8 bits). Fragments of tissues were fixed in 10.0% solution of neutral formalin, buffered with phosphate buffer. Subsequently, the material was subjected to standard wiring according to the standard of increasing concentration, chloroform, after which it was poured by paraffin. From the made paraffin blocks, serial slices were made in the thickness of 3-4 microns. In all cases, standard methods of coloring with hematoxylin and eosin were used.

The tumor cell phenotype was determined using low molecular weight cytokeratins (Cytokeratin PAN, AE1 / AE3), smooth muscle actin (Smooth Muscle Actin, 1A4), myogenin (Myogenin (F5D)), CD 10 and vimentin (Vimentin, V9). The primary monoclonal antibodies (MA) of DAKO (Denmark), Ready-to-Use, were used. To study the features of the extracellular matrix of the tumor and its metastatic potential, rabbit concentrated polyclonal antibodies (PA) were used for 1:50 dilution of matrix metalloproteinase-9 (MMP-9, 92kDa Collagenase IV) from Thermo scientific (Germany). Antibody de-masking was done by boiling in sections in citrate buffer (pH 6.0). UltraVision Quanto Detection Systems HRP Polymer (Thermo scientific) detection system was used to visualize primary antibodies. DAB (diaminobenzidine) was used as a chromogen. The results were counted with Avtandilov ocular grid [2] in 10 arbitrarily selected fields of view with an increase of 400x. The evaluation of the histochemical label was carried out in two parameters: the degree of prevalence and intensity of color, taking into account the severity of the reaction and its localization. The degree of distribution of the label was taken into account for the percentage content of cells positively colored in brown color from the total number of cells in the field of vision. To assess the color intensity, a qualitative scale was used: 0 - no reaction, 1+ - weak cytoplasmic coloration to 30.0% of tumor cells, 2+ - moderate reaction, 30.0 to 60.0% of stained cells, 3+ - pronounced cytoplasmic reaction in 60.0-100.0% of tumor cells. The complex of morphological studies was performed on a microscope Primo Star (Carl Zeiss) using AxioCam (ERc 5s) programs.

Statistical processing of the data was carried out using a program package "STATISTICA 10.0".

We express our gratitude to the staff of the Institute, Kherson Regional Oncology Center and Umea University, who participated in the treatment of the above-mentioned patients, as well as scientific research.

Results

Expression of MMP-9 was detected in 30 cases (55.5%), with a quarter of all 54 uterine sarcomas (25.9%) showing a marked reaction (3+). The largest number of 3+ tumors accounted for the share of LMS - 22.2% of the total, 66.7% - within the group (Table 1).

Table 1. Level of expression of MMP-9 in tumor tissue of uterine sarcoma of different histological types.

Expression level	LMS (n=18)	ESS (n=22)	US (n=14)	Total (n=54)
0	4 (22.2%) (7.4%)	16 (72.7%) (29.6%)	4 (28.6%) (7.4%)	24 (44.4%)
1+	0	0	6 (42.8%) (11.1%)	6 (11.1%)
2+	2 (11.1%) (3.7%)	4 (18.2%) (7.4%)	4 (28.6%) (7.4%)	10 (18.6%)
3+	12 (66.7%) (22.2%)	2 (9.1%) (3.7%)	0	14 (25.9%)

Notes: the first indices in% (in brackets) is the frequency with which this level of expression occurs among different subgroups (LMS, ESS, US), the second indices in% (in brackets) is the frequency with which this expression level is encountered in the total number of cases (n=54).

In these observations, colored granules of MMP-9 were located both in the cytoplasm of the tumor cells and in the endothelial cells of the tumor itself, in the endothelium of the myometrium vessels, in the lymphocytes, macrophages, histocytes of the infiltration zone of the tumor invasion zone in myometrium (Fig. 1).

Moderate (2+) staining of cytoplasm granules showed 18.6% of uterine sarcoma, this number included 4 cases of US and ESS (by 7.4% of all observations, 28.6 and 18.2% respectively, within groups) and 2 observations with LMS (3.7 and 11.1% within the group).

The reaction was determined fairly uniformly, and if the visualization of the patient with US was limited to tumor cells, the accumulation of MMP-9 in the LMS group was also found in the extracellular matrix. ESS demonstrated focal coloration of tumor parenchyma cells, endothelial platelets of blood vessels and reactive infiltrate cells (Fig. 2).

Weak and uneven (1+) reactions were in 11.1% of the observations, all of which were related to US (42.8% within the group).

In 2 of these cases, in the cytoplasm, sometimes in endothelial cells, expression could be considered as focal moderate, however, the enhancement of coloration (2+) was detected in only 10.0% of cellular elements.

In 44.4% of all sarcomas expression of MMP-9 was not detected. ESS accounted for 29.6% of MMR-9-negative tumors (72.7% of all ESS).

The results of MMP-9 expression, depending on the stage of the disease and on the presence or absence of relapse of the tumor, are distributed as follows (Table 2).

In none of the cases, the uterine sarcoma with MMP-9-negative (0) status (24 observations) did not show the progression of the tumor, as in I and II in the stages of the disease.

Expression of MMP-9 +1 was detected only in the US group: 3 of these tumors corresponded to stage I, 3 to stage II of the disease; relapses were not observed in any of these cases.

The level of coloring corresponding to 2+ at stage I was

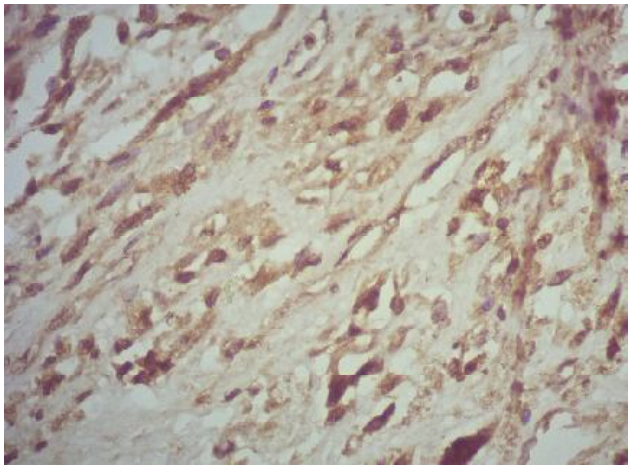

Fig. 1. The expressed cytoplasmic expression of MMP-9 in tumor cells, endothelial cells and extracellular matrix of leiomyosarcoma. Reaction with polyclonal antibodies on MMP-9, 92kDa Collagenase IV. x400.

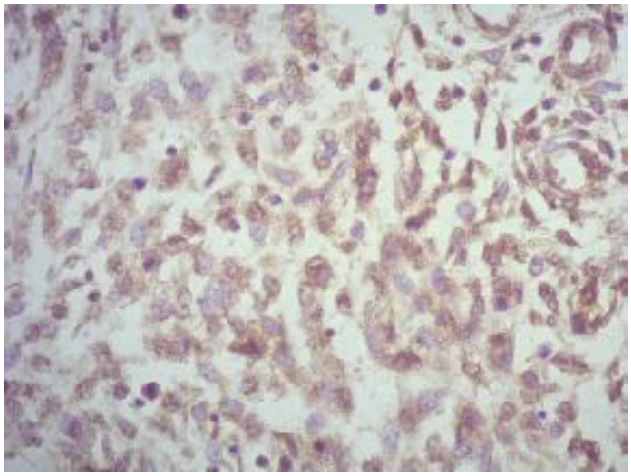

Fig. 2. Moderate cytoplasmic expression of MMP-9 in tumor cells, endothelial cells and reactive infiltrates of endometrial stromal sarcoma. Reaction with polyclonal antibodies on MMP-9, 92kDa Collagenase IV. x200.

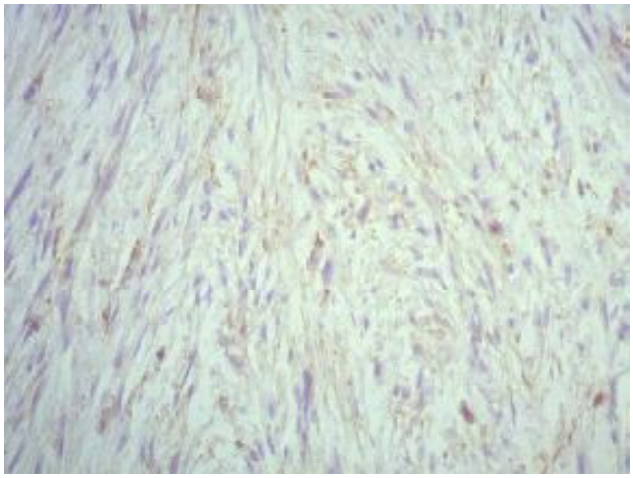

Fig. 3. Weak cytoplasmic expression of MMP-9 in tumor cells and the extracellular matrix of undifferentiated sarcoma. Reaction with polyclonal antibodies on MMP-9, 92kDa Collagenase IV. x200.

Table 2. Expression of MMP-9 in tumor tissue of the uterine sarcoma, depending on the stage of the disease and the presence of relapse.

	Stage of the disease	Presence of expression MMP-9	Presence of relapse
LMS (18)	T1 (16)	3+ - 12, 2+ - 2	4
		0 - 4	0
	T2 (2)	3+ - 2	2
ESS (22)	T1 (14)	3+ - 2, 2+ - 3	5
		0 - 9	0
	T2 (8)	2+ - 1	1
		0 - 7	0
US (14)	T1 (8)	2+ - 1, 1+ - 3	1 (2+)
		0-4	0
	T2 (6)	2+ - 3, 1+ - 3	3 (2+)
		0 - 0	0

detected in 1 case of US, 3 - ESS, and 2 - LMS, and, if the recurrence was noted at the US and ESS, then it was absent in the LMS. At stage II, moderate expression of MMP-9 was detected in ESS in 1 case, and in 3 cases with US; all of these patients had a recurrence of the disease.

Positive status (3+) MMP-9 is defined in 2 cases of ESS of stage I and in 14 LMS (12 - stage I, 2 - stage II). Recurrence of tumors is noted in two observations of the ESS. In LMS, the progression of tumors was detected in only two cases of stage I and two observations with stage II disease.

Discussion

In recent decades, many researchers have paid much attention to the study of proteolytic enzymes both in the tumor itself and in the surrounding extracellular matrix (ECM). It is known that the ability of tumor cells to invasive growth and distribution in the form of metastases depends on their properties to split the components of ECM - basal membrane, intercellular stroma, walls of blood and lymph vessels, as well as any components containing structural proteins [5, 6, 15]. The main role in the process of cleavage of structural proteins of ECM is played by the proteolytic enzymes of the matrix metalloproteinase (MMP) group, which are present both in the tumor and in the stromal cells. On the basis of currently accumulated scientific data, there is an impression that MMP are the major proteolytic enzymes that contribute to metastatic cancer cells [9, 11, 15]. Author Ganusevich I.I. established that MMP not only destroys ECM and basement membrane proteins, but also stimulates the migration of cellular tumors and plays a significant role in the survival of tumor cells that take part in the suppression of antitumor immunity and regulation of neo-angiogenesis, thereby providing additional pathways for the evacuation of primary tumor cells [7, 8].

The invasive activity of the tumor is supported by the increased enzymatic activity of the tumor or stromal cell, which secretes active MMP. Degradation and damage facilitates the allocation of tumor cells and their spread; therefore, MMP is a positive regulator of tumor invasion and growth [27, 38]. According to the Chiang A.C. experience, solid tumors have mechanisms that increase the ability of tumor cells to invade into the extracellular matrix, which promotes the formation of distant metastatic cells. Invasion of the tumor does not always lead to the formation of metastases; only about 0.01% of tumor cells initiate a more complex process of forming distant metastases [21]. Numerous studies, analyzed by Roy R., have shown a positive correlation between elevated levels of MMP in the tumor and the degree of invasion of tumor cells or the emergence of metastases [36].

Increased activity of MMP was detected in the progression of breast cancer, stomach, lung and other malignant diseases. The authors have shown that high expression of MMP-2 and MMP-9 is a significant factor in the adverse prediction of non-recurrent and total survival in cancer [21, 28, 37].

Solovyova N.I. with co-authors have shown that the main contribution to the invasive and metastatic potential of the squamous cell carcinoma of the cervix brings about an increase in the expression of collagenases of MMP-1 and MMP-14, of MMP-9 gelatinase and a decrease in the expression of TIMP-1 and -2 inhibitors [14]. This correlates with the results of other authors - the main role in the growth of invasive neoplastic cells in cervical cancer is played by matrix metalloproteinases (MMP) -1 and -2, the level of expression of which progresses with the growth of the tumor. In invasive carcinomas of the cervix, hyperexpression of MMP-9 is observed in the initial stages, which makes it possible to consider MMP-9 as a possible marker for early tumor diagnosis and its progression [12, 30, 40]. According to Abakumova T.B. with co-authors, in the process of tumor progression, the level of expression of MMP-9 is reduced. Expression of MMP-2 in serum of patients was elevated and correlated with the prevalence of the disease [1].

Hyperexpression of MMP-7 is described in a number of malignant neoplasms, such as breast cancer, lung, stomach, pancreas, head, neck and others [4, 26]. According to Laktionov K.P. with co-authors, in ovarian cancer, the level of MMP-7 in tumor tissue was significantly higher than in benign tumors, in contrast to the MMP-2 and -9 [13].

Barinov V.V. with co-authors, on the basis of the review of literature, showed that in case of cancer of the uterus body hyperexpression of several MMP (MMP-2, -7, -8, -9, -13) [4] was detected. In this case, elevated levels of the majority of MMP in tumor preparations did not correlate with metastatic lymph node involvement. At the same time, the expression of the level of matrilysin MMP-7 and MMP-9 is directly related to the degree of tumor invasion, its propensity to metastases, and unfavorable prognosis in patients with cancer of the uterine body [4].

Studies of the role of MMP in soft tissue sarcoma are devoted few studies [17, 35]. In her study, Benassi M.S. with co-authors, studied the role of various MMP in tumors of patients with fibromatosis and sarcoma of the extremities.

It was shown that the most pronounced expression in all tumors was noted for MMP-1, while the activity of TIMP-2 was higher in fibromatosis than in sarcomas. The authors believe that the state of MMP and TIMP determines the oncogenesis of tumors in soft tissues [17]. The prognostic role of MMP in the oncogenesis of sarcoma is confirmed by Roebuck M.M. with the co-authors, where the expression of MMP-2, MMP-9 and TIMP-2 was determined on the biopsy material of several histotypes of sarcoma (liposarcoma, synovial sarcoma and malignant tumor of the peripheral nerve shell). The authors showed that the dynamics of changes in the studied indicators has a prognostic value for the overall survival and duration of the non-recurring period in patients [35].

Dolzhikov A.A. with co-authors, showed that the growth of the expression level of MMP-9 is particularly pronounced in metastatic sarcomas [10].

After conducting studies on endometrial stromal sarcoma (ESS) and leiomyosarcoma (LMS) cell lines, Ravid Y. with co-authors showed the association of transcriptional regulation of MMP-2 activity and invasive tumor cell potential [33].

Bodner-Adler B. with co-authors study the expression of MMP on preparations of leiomyomas and leiomyosarcomas of the uterus. Significant overexpression was detected in MMP-1 in 86.0% of cases, for MMP-2 in 46.0% of cases [19]. There was a positive correlation between the level of MMP-2 expression and the presence of intravascular invasion. Statistically significant dependence of MMP-2 expression on the tumor stage and recurrence was not detected, however, in the group with MMP-2 negative status, the trend of more long-term, non-recurrent survival was found [18, 19].

Analysis of the above-mentioned works suggests that metalloproteinases-7, -9, -1, -2 are quite informative markers of soft tissue sarcomas.

In our study, expression of MMP-9 was found at 55.6%, regardless of the type of uterine sarcoma. Hyperexpression of MMP-9 is observed at 25.9% for leiomyosarcoma, in 11.1% for endometrial stromal sarcoma and 7.4% for undifferentiated sarcoma. At moderate and high levels of MMP-9 expression, recurrence of the tumor was noted in 61.5% of cases, which may indicate an invasive and metastatic tumor potential.

The study of changes in the content of MMP-9 in tumor tissue of the uterine sarcoma is promising, since its level may be useful for monitoring the course of the neoplastic process and the corresponding response to the treatment.

Conclusions

1. Negative (0) and weak positive (1+) expression of matrix metalloproteinase-9 was detected in 29.6% of ESS and 18.5% of US In any case, the relapse of the disease is not marked.

2. Moderate (2+) and high (3+) contents of MMP-9 were detected by us in 44.5% of uterine sarcoma, of which 26.4% of LMS. However, in cases of LMS, progression was observed only in the third observation (4 out of 12 cases), then in the ESS and US - in all cases.

3. With moderate and high content of MMP-9, the recurrence of the tumor was noted in 61.5% of cases, which may indicate an invasive and metastatic potential of the tumor.

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ЕКСПРЕСІЯ ММП-9 ЯК ФАКТОР ПРОГНОЗУ САРКОМ МАТКИ

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Саркоми тіла матки є високоагресивними мезенхімальними новоутвореннями, відмінністю яких є вкрай несприятливий прогноз. На сьогодні залишається актуальним питання пошуку клініко-морфологічних та біомолекулярних критеріїв прогнозу й безрецидивної виживаності при пухлинах матки. Відомо, що підвищення рівня експресії матриксної металопротеїнази-9 (ММП-9) у первинній пухлині чи метастазах корелює з низьким ступенем диференціювання пухлинних клітин, високим рівнем інвазивності пухлини, її високою метастатичною активністю, та скороченням тривалості життя пацієнток. Досі невідомо, чи можливо вважати експресію ММП-9 у клітинах сарком матки переконливим прогностичним фактором. Для багатьох типів епітеліальних злоякісних новоутворень високі показники метастазування пов'язують із зростанням рівня ММП-9 як в плазмі крові, так і у тканинній паренхімі. Метою даного дослідження є вивчення особливостей експресії ММП-9 у клітинах сарком матки для створення моделі індивідуального прогнозування перебігу захворювання. Проведено дослідження операційного матеріалу селекціонованих 54 випадків сарком матки I-II стадії (згідно критеріїв FIGO) з відомим прогнозом захворювання, котрі були розподілені залежно від морфологічного типу: лейоміосаркома (ЛМС) - 18 випадків, ендометріальна стромальна саркома (ЕСС) - 22 випадки, недиференційована саркома (НС) - 14 (згідно класифікації новоутворень матки ВООЗ). Для гістологічного дослідження висікали шматочки тканини з різних ділянок пухлинних вузлів - центральні, периферичні відділи, ділянки із прилеглої інтактної тканини міометрія (всього по 6-8 шматочків). Фенотип пухлинних клітин визначали за допомогою низькомолекулярних цитокератинів (Cytokeratin PAN, AE1/AE3), гладком'язового актину (Smooth Muscle Actin, 1A4), міогеніну (Myogenin (F5D)), CD 10 і віментину (Vimentin, V9). Гістохімічну мітку оцінювали за двома параметрами: ступінь розповсюдженості та інтенсивності забарвлення. Для оцінки інтенсивності забарвлення використовували якісну шкалу: 0 - відсутня реакція, 1+ - слабке цитоплазматичне забарвлення до 30,0 % пухлинних клітин, 2+ - помірна реакція, від 30,0 до 60,0 % забарвлених клітин, 3+ - виражена цитоплазматична реакція у 60,0-100,0 % клітин пухлини. Статистичну обробку отриманих даних здійснювали за допомогою пакета програм "STATISTICA 10.0". Проведене дослідження виявило, що негативна (0) та слабка позитивна (1+) експресія матриксної металлопротеїнази-9 відмічалася у більшості ЕСС та частині НС. Незалежно від стадії захворювання, з таким статусом ММП-9 не відмічено розвитку рецидиву. Помірний (2+) та високий (3+) вміст ММП-9 виявлений нами у 44,5 % сарком матки із явним переважанням при ЛМС. Однак, якщо у випадках ЛМС прогресія спостерігалась лише у треті спостережень (4 з 12 випадків), то при ЕСС та НС усі пухлини із таким статусом рецидивували. Подібна реакція може свідчити про інвазивний та метастатичний потенціал ЕСС та НС і обумовлює можливість розвитку гематогенних метастазів.

Ключові слова: *саркома матки, експресія ММП-9, взаємозв'язок експресії ММП-9 та прогресії пухлини, лейоміосаркома, ендометріальна стромальна саркома, недиференційована саркома.*

ЭКСПРЕССИЯ ММП-9 КАК ФАКТОР ПРОГНОЗА САРКОМ МАТКИ

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Саркомы тела матки являются высокоагрессивными мезенхимальными новообразованиями, отличием которых является крайне неблагоприятный прогноз. На сегодня остается актуальным вопрос поиска клинико-морфологических и биомолекулярных критериев прогноза и безрецидивной выживаемости при опухолях матки. Известно, что повышение уровня экспрессии металлопротеиназы-9 (ММП-9) в первичной опухоли или метастазах коррелирует с низкой степенью дифференцировки опухолевых клеток, высокой степенью инвазивности опухоли, ее высокой метастатической активностью, сокращением продолжительности жизни пациенток. До сих пор неизвестно, можно ли считать экспрессию ММП-9 в клетках сарком матки убедительным прогностическим фактором. Для многих типов эпителиальных злокачественных новообразований высокие показатели метастазирования связывают с ростом уровня ММП-9 как в плазме крови, так и в тканевой паренхиме. Целью данного исследования является изучение особенностей экспрессии ММП-9 в клетках сарком матки для создания модели индивидуального прогнозирования течения заболевания. Проведенное исследование операционного материала селекционированных 54 случаев сарком матки I-II стадии (согласно критериев FIGO) с известным прогнозом заболевания, которые были разделены в зависимости от морфологического типа: лейомиосаркома (ЛМС) - 18 случаев, эндометриальная стромальная саркома (ЭСС) - 22 случая, недифференцированная саркома (НС) - 14 (согласно классификации новообразований матки ВОЗ). Для гистологического исследования высекали кусочки ткани из разных участков опухолевых узлов - центральные, периферические отделы, участки из прилежащей интактной ткани миометрия (всего по 6-8 кусочков). Фенотип опухолевых клеток изучали при помощи низкомолекулярных цитокератинов (Cytokeratin PAN, AE1/AE3), гладкомышечного актина (Smooth Muscle Actin, 1A4), миогенина (Myogenin (F5D)), CD 10 и виментина (Vimentin, V9). Гистохимическую метку оценивали по двум параметрам: степень распространения и интенсивности окраски. Для оценки интенсивности окрашивания использовали качественную шкалу: 0 - отсутствует реакция, 1+ - слабое цитоплазматическое окрашивание до 30,0 % опухолевых клеток, 2+ - умеренная реакция, от 30,0 до 60,0 % окрашенных клеток, 3+ - выраженная цитоплазматическая реакция у 60,0-100,0 % клеток опухоли. Статистическую обработку полученных данных осуществляли с помощью пакета программы "STATISTICA 10.0". Проведенное исследование показало, что отрицательная (0) и слабая положительная (1+) экспрессия матриксной металлопротеиназы-9 отмечалась в большинстве ЭСС и части НС. Независимо от стадии заболевания, с таким статусом ММП-9 не отмечено развития рецидива. Умеренное (2+) и высокое (3+) содержание ММП-9 обнаружено нами в 44,5 % сарком матки с явным преобладанием при ЛМС. Однако, если в случаях ЛМС прогрессия наблюдалась лишь в трети наблюдений (4 из 12 случаев), то при ЭСС и НС все опухоли с таким статусом рецидивировали. Подобная реакция может свидетельствовать об инвазивном и метастатическом потенциале ЭСС и НС и обусловливает возможность развития гематогенных метастазов.

Ключевые слова: *саркома матки, экспрессия ММП-9, взаимосвязь экспрессии ММП-9 и прогрессирование опухоли, лейомиосаркома, эндометриальная стромальная саркома, недифференцированная саркома.*