Original paper

Research on genesis of adipocytic metaplasia in uterine fibroids

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The genesis of lipoleiomyoma has not been explained yet. Immunohistochemical examinations were performed on 17 lipoleiomyomas in women aged 43-82 (mean age: 51 ±9 years). Four types of myomas were distinguished: 1) pure leiomyoma, 2) fibroleiomyoma, 3) hyalinizing leiomyoma, 4) strongly hyalinized myoma, along with three degrees of progression of adipocytic metaplasia: 1) up to 25% of lipocytes, 2) up to 50% of lipocytes, and 3) over 50% of lipocytes in the analyzed sample, along with three degrees of progression of adipocytic metaplasia: 1) up to 25% of lipocytes, 2) up to 50% of lipocytes, and 3) over 50% of lipocytes in the analyzed sample.

A positive correlation was found between the age of women and rate of development of metaplasia ($r = 0.51$, $p = 0.035$) as well as with activity of the estrogen receptor in the primary tumor ($r = 0.53$, $p = 0.03$).

New mucous perivascular tissue was reported among 11.8% of patients and on this basis lipocytes were formed.

The appearance of subendothelial granular cells of large blood vessels with a positive reaction for smooth muscle actin (SMA) and CD68 was reported in 17.7%.

Results of immunohistochemical research seem to confirm that lipocytes *de novo* come from the primal pluripotent cells of the tumor stroma and not from the fatty degeneration of myocytes.

Key words: uterus, lipoleiomyoma, histogenesis, immunohistochemistry.

Introduction

Uterine fibroids with adipocytic metaplasia are rare in women. According to our previous studies they appeared in 1.33% of all performed hysterectomies [1].

The histogenesis of these changes arouses controversy [2, 3, 4]. Immunohistochemically, the examined lipocytes always yielded a positive reaction with S-100 antibody [5, 6], and a negative reaction with muscle antibodies [5, 6, 7]. According to Aung *et al.* [4], the majority of the lipomatous component in the uterine fibroids yielded a negative reaction with SMA antibodies, but in some parts lipocytes showed SMA positivity. There were fewer estrogen and progesterone receptors in lipoleiomyomas than in surrounding uterine corpus muscle [8, 9], which may indicate the role of hormonal disorders in their histogenesis.

In current research we decided to follow the development of adipocytic metaplasia process in uterine fibroids depending on: 1) the age of patients, 2) the type of the primary tumor stroma in which the process of metaplasia took place, 3) the participation of estrogen and progesterone receptors in the primary tumor.

Table I. Primary antibodies used in the study (all from DAKO)

No.	Specificity	Clone/Type	Dilution
1.	S-100	Polyclonal	1 : 1000
2.	SMA	1 A4	1 : 100
3.	Desmin	D 33	1 : 100
4.	CD34	QBEnd 10	1 : 100
5.	D2-40	D2-40	1 : 100
6.	ER	EP1	1 : 100
7.	PG	PgR 636	1 : 100
8.	CD117	A 4502	1 : 300
9.	CD68	PG - N1	1 : 100
10.	Ki-67	MIB-1	1 : 100
11.	WT 1	6F-H	1 : 100
12.	Cytokeratin 5/6	D5/16B4	1 : 100
13.	FVIII	kat. 1505	producer's dilution
14.	Thrombomodulin	1009	1 : 100
15.	Calretinin	DAK – Calret 1	1 : 100
16.	Vimentin	V 9	1 : 100
17.	Melanosome	HMB 45	1 : 100

Material and methods

The archive material originating from 17 uteri with previously diagnosed foci of adipocytic metaplasia was used in the examination. Age of patients ranged between 43 and 82 years, with the average age of 51.0 ±9 years.

Paraffin sections were cut at 4 μm. In addition to hematoxylin and eosin staining, sections were stained with the Mallory method and with toluidine blue. Moreover, in selected cases, they were stained with periodic acid – Schiff (PAS), with alcian blue and with Grocott-Gomori methenamine silver staining. Immunohistochemical reactions were performed on all the specimens numbered 1-8 presented in Table I, and also 10 times with CD68 and NSE, 9 times with Ki-67, and 7 times with WT1, CK 5/6 and FVIII.

Reactions to thrombomodulin, calretinin and vimentin were conducted 5 times. HMB 45 staining was conducted four times.

Four types of myomas were classified from the material: 1) pure leiomyoma, 2) fibroleiomyoma, 3) hyalinizing leiomyoma, 4) strongly hyalinized myoma.

The degree of adipocytic metaplasia was determined as: 1) if the percentage of lipocytes in the histological specimen was 25%, 2) if the percentage of lipocytes was between 25% and 50%, 3) if the percentage of lipocytes was over 50%.

Immunohistochemical reactions were conducted according to standards of the local laboratory. Paraffin sections were placed on silanized slides (DAKO cat. S 3003), deparaffinized in xylene and then passed through a descending alcohol series into water.

Antibodies of tissues fixed in formalin were discovered in Target Retrieval Solution (DAKO cat. 3307) by heating at 96 degrees for 20 minutes. Endogenous peroxidase was blocked in 3% H_2O_2 solution for 10 minutes. Primary antibodies were placed on paraffin sections. Sections were rinsed in TBS. The visualization system En Vision + HRP (DAKO cat. 4007) was put on sections, which were later incubated for 30 minutes at room temperature. The immunohistochemical reaction was carried out with a solution of 3.3'-diaminobenzidine tetrachloride (DAB, liquid K 3486 DAKO). Next, the sections were rinsed in running water and graded alcohol dehydration was performed. The material was then exposed in xylene and encased in balm. The evaluation of staining intensity was half-quantitative according to the following gradation: 0 – lack of positive reaction, 1 – weak reaction, 2 – strong reaction. The final evaluation of the separate reactions was based on the average taken from the three readings carried out at monthly intervals. In this way, the results (in figures) were subject to statistical analysis with the Statistica 9 program. Differences at the $p \leq 0.05$ level were considered significant.

Results

The results of the study are depicted in Tables II-IV. According to Table II, 41% were pure myomas, 23.5% were fibroleiomyomas and 17% were hyalinizing leiomyomas and strongly hyalinized myomas.

58.8% of tumors exhibited adipocytic metaplasia in early phases of development: 35.3% in a semi- advanced phase, and 5.9% in a very advanced phase.

Table III and Figure 1 show that the dynamism of adipocytic metaplasia in myoma was positively correlated with the individual age of patients ($r = 0.514$, $p = 0.035$). This dynamism depended also on the activity of the estrogen receptor in myoma ($r = 0.53$, $p = 0.030$), but it was not correlated with the activity of the progesterone receptor, nor with the type of regressive changes in the primary tumor (Table IV, Figure 2). Adipocytes presented a close relation to blood vessels (Fig. 3). Some delicate connective tissue component around lipocytes was always reported in staining with the Mallory method and in the reaction with vimentin, even in "full" myomas. Cells of this type were always S-100 positive (Fig. 4). Inflammatory infiltrate composed of acidophilic granulocytes (Fig. 5) was sometimes observed around blood vessels and lipocytes. Mast cells were more visible after reac-

Table II. Age of women, tumor type, lipid metaplasia and value of some immunocytochemical reactions

No.	Sample number	Age	Tumor type	Lipid metaplasia	S-100	SMA	Desmin	E-r	Pg-r
1.	4032	50	1	1	0.00	0.83	0.00	0	1
2.	7595/01	43	1	1	0.00	1.00	0.30	0	2
3.	14327	49	1	1	0.00	0.80	0.00	1	2
4.	12760	57	1	1	1.00	0.83	0.20	0	0
5.	13423	50	1	1	0.00	1.00	0.30	0	1
6.	50208	46	1	1	0.00	0.70	0.70	1	1
7.	38218	43	2	1	0.50	2.00	2.00	0	2
8.	5929-37	43	3	1	1.00	0.70	0.30	0	2
9.	22604	55	4	1	1.00	0.70	0.70	2	2
10.	39238	45	4	1	2.00	2.00	2.00	1	2
11.	9/01	82	1	2	2.00	1.00	0.70	1	2
12.	13337-8	50	2	2	1.00	1.33	0.33	1	2
13.	13168	50	2	2	2.00	0.70	0.20	2	2
14.	48362	52	3	2	2.00	0.80	1.33	2	2
15.	12470	51	3	2	2.00	1.00	0.20	1	2
16.	5679	46	4	2	1.00	1.70	1.00	0	2
17.	45789-802	61	2	3	1.00	1.33	1.33	2	1
			Type 1 = = 41.2%	Type 1 = 58.8%					
	X + SD	51.4 + 9.4	Type 2 = = 23.5%	Type 2 = 35.3%	0.97 + 0.80	1.08 + 0.44	0.68 + 0.64	0.82 + 0.81	1.65 + 0.61
			Type 3 = = 17.6%	Type 3 = 5.9%					
			Type 4 = = 17.6%						

SMA – smooth muscle actin, E-r – estrogen receptor, Pg-r – progesterone receptor, x – medium value, SD – standard deviation, tumor type – see Material and methods, lipid metaplasia – see Material and methods.

tion with CD117 than after staining with toluidine blue. Mast cells were almost always present in uterine stroma and around lipocytes. Reaction with antibody CD68 was strongly positive in 8.3% of cases (Fig. 6). An identical proportion to this reaction was however weakly positive. In fibrous and hyaline masses of the primary tumor, we observed the spontaneous creation of lipocytes with SMA positive circumference of those cells (Fig. 7) and strongly positive reaction for S-100 antibody (Fig. 8). Positive reaction with Ki-67 antibodies (Fig. 9) was reported twice in primary tumor (11.8%) and once in lipocytes (5.9%). In the examined material we reported that in the case of two women (11.8%) young mucous tissue developed out of fibrotic myoma masses on which formed lipocytes. These changes took place in close connection with capillaries (Figs. 10, 11). In myomas in three women (17.65%) (women numbered 8, 15, 16) under the endothelium of large blood vessels the appearance of polygonal cells with a centrally located nucleus and a large amount of amphoteric granules (Figs. 12, 13) was reported. These cells were always SMA positive (Figs. 14-16). They were proliferating strongly and moving the endothelium to the vessel lumen, closing it more than once (Figs. 15, 16). Among other reactions, these cells were CD68 positive (Fig. 17), they reacted poorly with toluidine and S-100, they did not stain with desmin (Fig. 18), and they gave a negative reaction with CD117 and HMB 45. Reactions with calretinin were carried out 5 times. In 40% of the cases, the reaction was positive in isolated cells of the main tumor (Fig. 19). Once there was intensive staining of the lipocyte circumference in a 61-year-old woman numbered 17 (Fig. 20).

Reactions with vimentin were always positive, with antibody D2-40 always negative. Reactions with WT1, CK5/6, thrombomodulin and NSE were always negative.

Table III. Spearman rank correlation coefficient with marked p-value at significance level equal to 0.05

	Issue	N	R	t (N-2)	p
Age &	Tumor type	17	–0.095	–0.368	0.718
	Lipid metaplasia	17	0.514	2.32	0.035
	S-100	17	0.408	1.729	0.104
	SMA	17	–0.137	–0.538	0.599
	Desmin	17	–0.084	–0.328	0.748
	E-r	17	0.519	2.349	0.033
	Pg-r	17	–0.307	–1.248	0.231
Tumor type &	Lipid metaplasia	17	0.277	1.118	0.281
	S-100	17	0.589	2.825	0.013
	SMA	17	0.163	0.640	0.532
	Desmin	17	0.499	2.232	0.041
	E-r	17	0.316	1.292	0.216
	Pg-r	17	0.543	2.501	0.024

N – number of observation, R – Spearman rank correlation coefficient, t (N-2) – test statistics of Student distribution with N-2 degrees of freedom, p – probability value of test statistics, tumor type – see Material and methods, lipid metaplasia – see Material and methods, S-100 – prot in S-100, SMA – smooth muscle actin, E-r – estrogen receptor, Pg-r – progesterone receptor.

Summing up, immunohistochemical staining in lipocytes varied depending on the tumors.

The reaction with actin antibody (group average of 1.08 points) was the strongest, while the reaction with S-100 (0.97 points) and desmin (0.68 points) was weaker.

Discussion

In 1955 Brandfass and Everts-Suarez [10] quoted from academic literature 7 theories concerning the origin of uterine lipoleiomyomas. They also wondered whether pure forms of lipomas had the same genesis as mixed forms. According to the authors, pure forms may originate in stray mesenchymal cells of stroma, and mixed forms appear as a result of fat degeneration of myocytes. Similar suggestions were made by Meinhof and Bersh [11]. However, they were contradicted by Salm [12]. According to this author, lipoleiomyomas were never observed in children and adolescents. On the other hand, mixed forms appear usually before menopause, and pure forms after menopause. Similar observations were made in our previous work [1]. It may be concluded from the above data that mixed forms, constantly growing, eventually lead to the appearance of "pure" forms.

In our current research we observed the development of lipocytes in the connective tissues situated close to the blood vessels. Negative results with D2-40, WT1 and with other antibodies [13, 14] ruled out the possibility that lymphatic vessels and mesothelium of peritoneum took part in their development.

According to other authors [2, 15], immunohistochemical reactions carried out in lipoleiomyomas gave various results, staining uterus myocytes SMA positive and adipocytes S-100 positive. No transitory forms have been observed between myocytes and

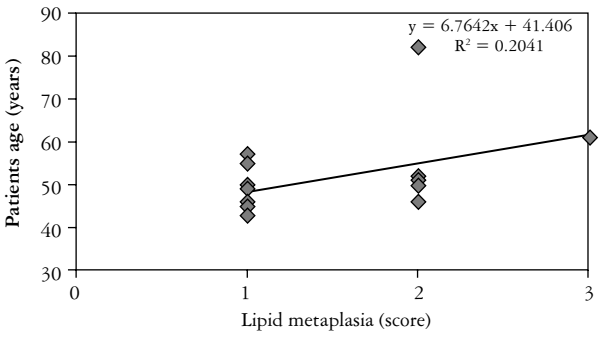

Fig. 1. Scatter diagram of patients' age vs. lipid metaplasia

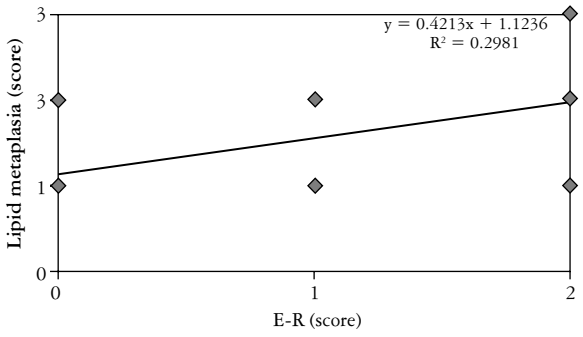

Fig. 2. Scatter diagram of lipid metaplasia vs. estrogen receptor

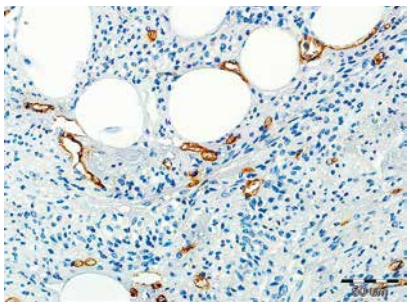

Fig. 3. Lipocytes in near vicinity to CD34 positive capillaries 400×

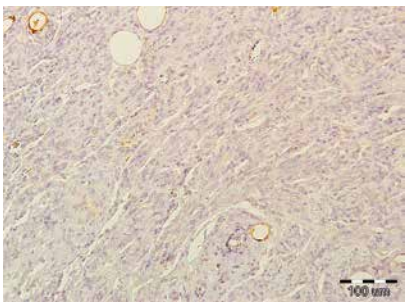

Fig. 4. Some dispersed S-100 positive lipocytes in uterine myoma 200×

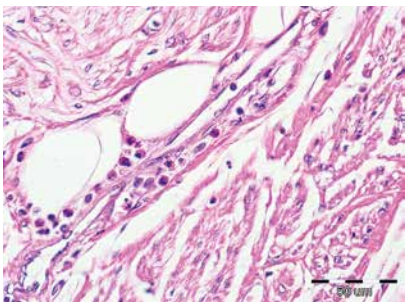

Fig. 5. Eosinophils arranged around some lipocytes, HE 600×

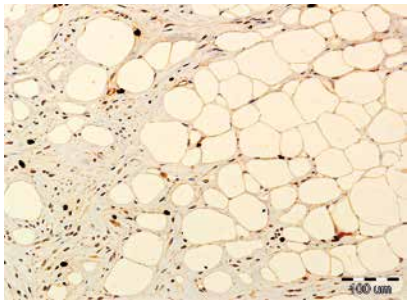

Fig. 6. CD68 positive reaction in the uterine stroma and around some lipocytes 200×

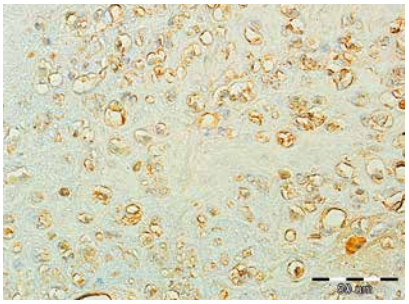

Fig. 7. Multiple newly formed lipocytes in a fibrotic focus of leiomyoma. SMA positive circumference of those cells 600×

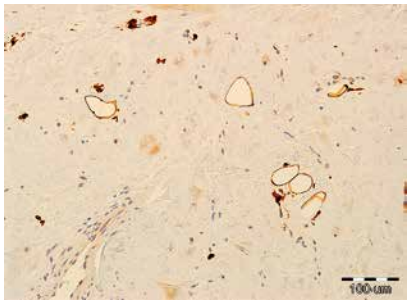

Fig. 8. S-100 positive reaction of lipocytes in a hyalinized focus of the leiomyoma 200×

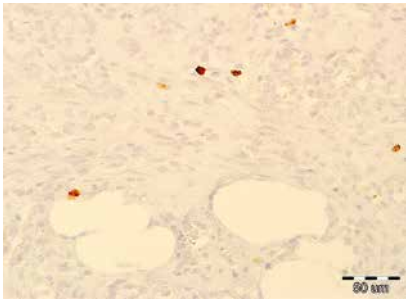

Fig. 9. Ki-67 positive cells in the interstitium of a lipoleiomyoma and surrounding some lipocytes 600×

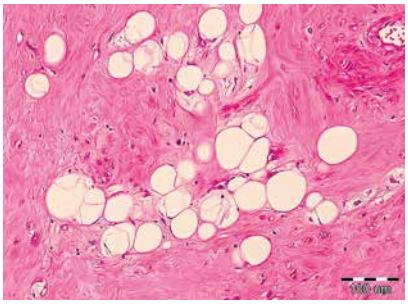

Fig. 10. Muco-lipomatous metaplasia focus in a fibrotic uterine leiomyoma, HE 600×

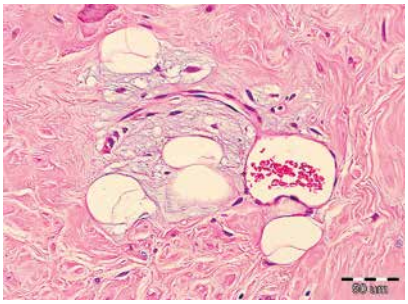

Fig. 11. Metaplasia mucino-lipomatosa near an unchanged vessel of a fibrotic lipoleiomyoma, HE 600×

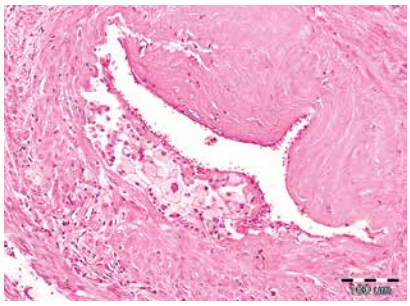

Fig. 12. Subendothelial located amphoteric granulated cells of a big vessel in hyalinized leiomyoma, HE 400×

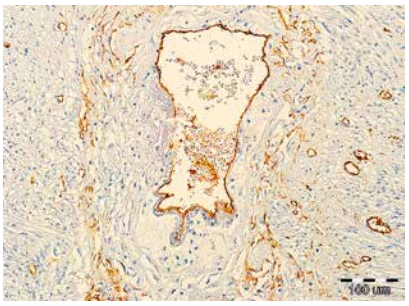

Fig. 13. The same cells as in Fig. 10 around an unchanged vessel. Positive CD34 reaction in the vessel wall 400×

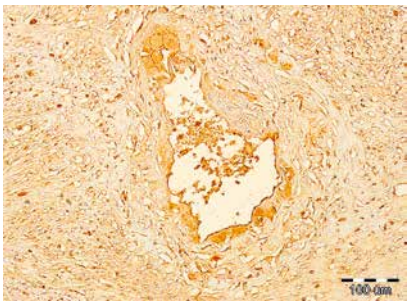

Fig. 14. The same case as in Fig. 11 with SMA positive granules in the mentioned cells 400×

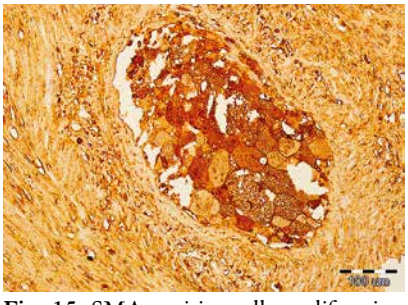

Fig. 15. SMA positive cells proliferating and occluding the vessel lumen 400×

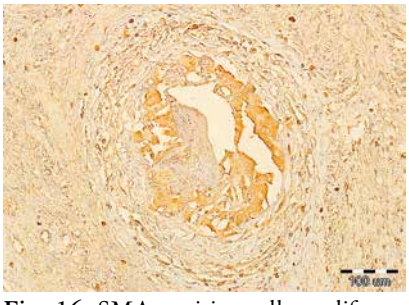

Fig. 16. SMA positive cells proliferating into the vessel lumen 400×

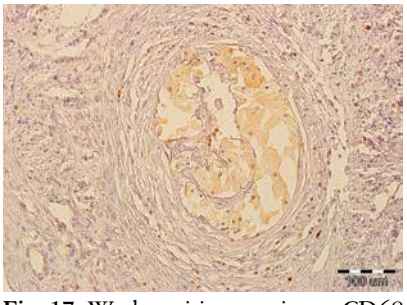

Fig. 17. Weak positive reaction to CD68 antibodies in the same cells as in Fig. 14 400×

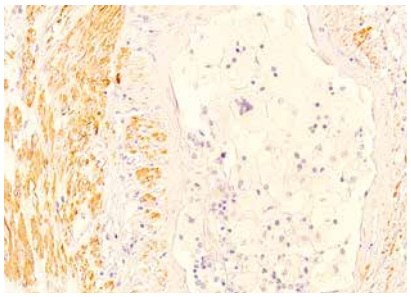

Fig. 18. Negative reaction to desmin of the mentioned cells 400×

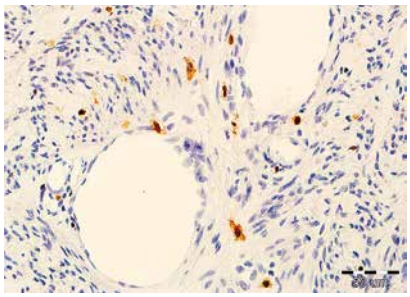

Fig. 19. Some calretinin-positive cells in the interstitium and around lipocytes of a lipoleiomyoma 600×

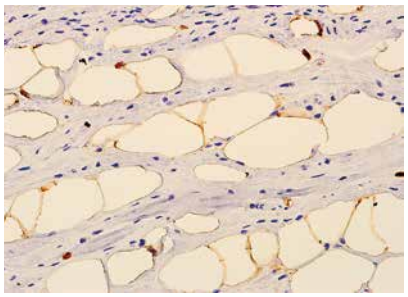

Fig. 20. Calretinin-positive lipocytes (the same case as in Fig. 4) 400×

lipocytes [3], which provided grounds to reject the hypothesis that the developed lipocytes in uterine fibroids were of a degenerative nature and instead supported the hypothesis of them being cancerous in nature [12]. It is assumed that there are mesenchymal totipotential pericapillary cells [2, 16, 17], with numerous possibilities of diversification, including those necessary to create lipocytes [2, 3, 9], which eventually lead to the occurrence of adipocytic neometaplasia [9, 15] and eventually to the development of lipoma in the uterus [12]. Lipocytes developed this way are characterized by a high proliferative index Ki-67, which supports their cancerous, not degenerative nature [4, 15]. Cytogenetic examinations of lipoleiomyomas in the uterus indicated the possibility of different components of the primary tumor existing [18, 19]. That is why the type of components found in uterine fibroids depends only on the accuracy of research and on the number of sampled tissues of the main tumor [20].

Ultrastructural examination of myxomas revealed that myofilaments are present in myxoma cells [17]. They were particularly exposed in cells close to the vessel wall. The results of our research were compatible with the data cited above from the academic literature. Spontaneous development of lipocytes in the stroma of fibromatous, or even hyalinized myoma, is a surprising phenomenon. These cells were both SMA and S-100 positive. The creation of mucous tissue around the vessels and based on it formation of lipocytes was particularly interesting. Positive reaction with Ki-67 antibodies in myoma cells as well as in lipocytes of our material confirms the suggestions of the academic literature about the cancerous character of formed lipocytes. Granulated subendothelial cells of large blood vessels, containing both muscle antigens and antigens which characterize phagocytic cells, are the second important element we observed in our examination. There is a question whether they represent the inflammatory reaction to the creation of regressive changes in the wall of blood vessels, or they are primal changes, reverting from myocytes to lipocytes as mentioned by Mazur and Kraus [17]. These are not mast cells or cells from the PEComa group, which is confirmed by negative staining results for HMB 45 and CD117. However, they were CD68 positive. According to Resta *et al.* [15], no positive reaction to CD68 and MAC 387 was ever reported in the examined lipoleiomyomas. We carefully analyzed the available literature and we did not find similar descriptions.

The presence of mastocytes was reported in almost all analyzed specimens in the whole visual field. They were localized not only in the tumor pulp, but also around lipocytes. Their role in carcinogenesis is controversial [5, 21, 22, 23, 24].

According to Özdemir *et al.* [23], it should be asked whether they are an active player in the process of adipocytic "neometaplasia" of uterine fibroids, or they are just a harmless "passerby". In our current material they appeared most frequently in lipoleiomyoma with the most advanced metaplasia in the 61-year-old woman (case 17).

Kinins are released as a result of changes in the environment of the main tumor, such as hyperemia, exudate and other regressive changes, and mastocytes play a significant role in these processes [24]. It is possible that interactions between these components could have stimulated the pluripotential cells already existing in mesenchymal stroma to create lipocytes. In the current research, the formation of such lipocytes was noted even in a strongly hyalinized stroma. However, this phenomenon was not statistically significant.

The hormonal state of a woman with adipocytic metaplasia in uterine fibroids requires further research. Sieinski *et al.* [9, 25] recorded a higher concentration of estrogen and progesterone receptors in uterine fibroids than in the surrounding muscle of the uterine corpus. Akpolat *et al.* [8] reported in a 54-year-old woman fewer estrogen receptors in lipoleiomyoma than in the surrounding muscle of the uterus. In our own material, we observed a positive correlation between the quantity of estrogen receptors in the primary tumor and the rate of development of adipocytic metaplasia. This correlation was

additionally positively related with the individual age of operated patients. However, in comparison with the quantity of progesterone receptors, as well as in comparison with the degree of regressive changes in the main tumor, as mentioned above, such a correlation was not demonstrated. Similar research carried out on a larger scale and with more precise biochemical methods needs to be performed.

Conclusions

The rate of development of adipocytic metaplasia in uterine fibroids is positively correlated with the age of patients.

Increased activity of estrogen receptors in primary tumor supports rapid development of adipocytic metaplasia in the uterine fibroid.

Immunohistochemical examination results suggest that adipocytes in uterine fibroids come from multipotential stroma cells.

Type of regressive changes in uterine fibroids was not significantly correlated with the rate of adipocytic metaplasia in primary tumor.

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The authors declare no conflict of interest.

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