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DISTAL COLONIC POLYPS: IMMUNOHISTOCHEMICAL STUDY OF PROLIFERATION AND APOPTOSIS

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ABSTRACT. Background. It's well known that colonic polyps can be precursors of colorectal cancer. But exact immunohistochemical parameters, including proliferation and apoptosis levels of polyps' cells, that may have prognostic value, still not known. **Objective.** To study the features of immunohistochemical expression of proliferation and apoptosis markers by distal colonic polyps' cells. **Methods.** Pathomorphological and immunohistochemical studies of biopsies of distal colonic polyps from 30 patients (the age ranged from 41 to 83 years) were carried out. **Results.** Distal colonic polyps are characterized by the medium proliferation level of epithelial cells [Me=62.40% (48.65; 76.23) for adenomas, Me=26.23% (22.19; 48.88) for hyperplastic polyps], the low proliferation level of stromal cells [Me=2.94% (1.23; 4.35) for adenomas, Me=1.18% (1.10; 1.86) for hyperplastic polyps], the low p53 expression level of epithelial and stromal cells [Me=2.39% (1.58; 8.26) and Me=1.23% (0.72; 1.49) for adenomas' cells, Me=0,00% (0,00; 1,47) and Me=0,00% (0,00; 0,05) for hyperplastic polyps' cells], and also by the low apoptosis level of epithelial and stromal cells [Me=31.84CUOD (19.53; 42.34) and Me=43.87CUOD (25.47; 73.09) for adenomas, Me=16.99CUOD (11.86; 39.85) and Me=28.64CUOD (19.20; 30.71) for hyperplastic polyps]. There are direct correlations between the expression levels of proliferation and apoptosis markers and also the dysplasia grade of the distal colonic adenomas: between the Ki-67 expression levels of epithelial and stromal cells and also the dysplasia grade (γ=0.65 and γ=0.70, respectively), between the p53 expression level of epithelial cells and the dysplasia grade (γ=0.53), between the caspase-3 expression levels of epithelial and stromal cells and also the dysplasia grade (γ=0.80 and γ=0.63, respectively). Moreover, there are direct correlations between the expression levels of proliferation and apoptosis markers of distal colonic polyps' epitheliocytes: between the Ki-67 and p53 expression levels (r=0.71 for adenomas, r=0.79 for hyperplastic polyps), between the Ki-67 and caspase-3 expression levels (r=0.61 for adenomas), between the p53 and caspase-3 expression levels (r=0.59 for adenomas, r=0.79 for hyperplastic polyps). **Conclusion.** These data indicate the close association between the processes of proliferation, accumulation of p53 protein, and apoptosis of the distal colonic polyps' cells.

Key words: polyps, colon, cell proliferation, apoptosis, tumor suppressor protein p53, caspase-3.

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Introduction

Three possible ways of colorectal cancer (CRC) development are known: «adenoma – carcinoma» sequence is a mechanism of development for 50-70% CRC cases, serrated pathway is a mechanism of development for 30-35% CRC cases, Lynch syndrome is a mechanism of development for 3-5% CRC cases [1]. This division is based on clinical, morphological, and molecular-genetic heterogeneity of pre-tumor processes as well as the following stages of carcinogenesis [1, 2].

Epithelial polyps are essential among pre-tumor processes in colon [3]. According to the current WHO classification (2010) colonic epithelial polyps are divided into adenomas (tubular, villous, tubulovillous) and serrated polyps (hyperplastic polyps, traditional serrated adenomas, sessile serrated adenomas) [4].

Colorectal adenomas are considered as a variant of intraepithelial neoplasia. They are characterized by dysplastic changes of epithelium; namely adenomas have the greatest malignant potential among all the types of colonic polyps [5]. It's currently known that malignization of colorectal adenomas is realized during the "adenoma – carcinoma" sequence, molecular-genetic basis of which is made up of *CIMP*-phenotype (*CpG island methylator phenotype*), microsatellite stability (*MSS)* or low level of microsatellite instability *(MSI-low)*, as well as the absence of BRAF and KRAS genes mutations [1, 2].

Serrated polyps are distinguished by typical serrated (jagged, sawtooth) appearance of crypts and their epithelial cover. Previously, only hyperplastic polyps were known as serrated polyps; moreover, it was believed that they didn't have malignant potential [6, 7]. During the last 10 years it was revealed that serrated polyps are heterogenous group of neoplasms which can be precursors for CRC. *CIMP*-phenotype, low or a high microsatellite instability level (*MSI-low / MSI-high*), BRAF and KRAS genes mutations are the basis for serrated pathway of malignization [1, 2].

Activation of cell proliferation mediated by proto-oncogenes combined with inactivation of apoptotic cell death mediated by tumor-suppressor genes is one of universal molecular characteristics of carcinogenesis [5]. The features of proliferation and apoptosis in CRC were studied in the number of studies [8-10] including the work carried out in the context of this study [11-12], while the question of features of proliferation and apoptosis in colon polyps which are precursors of CRC weren't elaborated.

Research objective – to study the features of immunohistochemical expression of proliferation and apoptosis markers by the distal colonic polyps' cells.

Subject and methods

Pathomorphological and immunohistochemical studies of biopsies of distal colonic polyps from 30 patients (the age ranged from 41 to 83 years) were carried out.

The paraffin sections, that were obtained on the Microm HM 340E precision rotary microtome (Thermo Scientific, USA), were colored by hematoxylin and eosin, and by PAS-reaction. These sections were examined under the Axioplan 2 microscope (Carl Zeiss, Germany) with the purpose to explore microstructure of the polyps, to estimate the histological type of each polyp according to the current WHO classification [4], and to reveal dysplastic changes.

Immunohistochemical study (IHC) study was performed according to the standard procedures, that were developed by the manufacturers of antibodies. The monoclonal antibodies Mo a-Hu Ki-67 Antigen (Clone MIB-1, DAKO, Denmark), Mo a-Hu p53 Protein (Clone DO-7, DAKO, Denmark), Mo a-Hu Caspase Ab-3 (Clone 3CSP03, Thermo Scientific, USA), and the visualization system EnVisionFLEX with Diaminobenzidine were used. Results of the IHC study were evaluated using the Axioplan 2 microscope (Carl Zeiss, Germany); microslides were photographed by digital camera "Canon EOS 1000D" (Japan) with an increasing of x200, in five fields of view in each case.

The nuclear expression of Ki-67 and p53 markers was evaluated using Photoshop CC (2014) in digital images of the microslides. The Ki-67 expression level was estimated as low if it was less than 25% of immunopositive cells in a field of view, the expression level was estimated as medium if it was 25-75% of immunopositive cells in a field of view, and the expression level was estimated as high if it was more than 75% immunopositive cells in a field of view. Expression level of p53 was determined and graduated in the same way.

The nuclear-cytoplasmic expression of caspase-3 was evaluated using the digital morphometry method [13]. The caspase-3 expression level was expressed in the conventional units of the optical density (CUOD) and was graduated on the four levels: the lack of expression – 0-20 CUOD, the low caspase-3 expression level – 21-50 CUOD, the moderate – 51-100 CUOD, and the high caspase-3 expression level – more than 100 CUOD.

Statistical processing of the results was performed on a personal computer using program "Statistica® for Windows 6.0" (StatSoft Inc., License №AXXR712D833214FAN5). The median (Me), the lower and the upper quartiles (Q1; Q3) were calculated. Comparison was performed using the Mann-Whitney U-test and the Kruskal–Wallis test by ranks. The study of correlations between the studied parameters was performed using Spearman's rank correlation coefficient (r) and the Gamma coefficient (γ) The results were considered as statistically significant when $p<0.05$.

Research results and discussion

According to the results of pathohistological study it was revealed that 73,33% from all the distal colonic polyps (DCP) presented by adenomas, 26,67% – hyperplastic polyps. Herewith, 59,09% from all the adenomas presented by tubular adenomas, 18,18% – villous adenomas, and 22,73% – tubulovillous adenomas. These data are shown in the Fig. 1.

Adenomas consist of branching glandular structures that surrounded by loose connective tissue. Villous adenomas are distinguished by typical rod-shaped fibrous villi with epithelial cover; tubulovillous adenomas are characterized by presence of tubular and villous glandular structures within one polyp. In 56% of adenomas the low-grade dysplasia was revealed, in 44% – the high-grade dysplasia was revealed.

Hyperplastic polyps are distinguished by proliferation of the surface epithelium cells as well as the cells of mucosa glands with extension of tubular structures. A typical serration is more expressed in superficial parts of the polyps, whereas an expansion of proliferation zone is expressed mostly in the basal parts of crypts. The dysplastic changes weren't revealed in the hyperplastic polyps.

According to the results of IHC study it was revealed that the DCP are characterized by the medium proliferative activity level of epitheliocytes [the median of Ki-67 expression level in adenomas was 62,40% (48,65; 76,23), in hyperplastic polyps – 26,23% (22,19; 48,88), ($p<0,05$)] as well as by the

low medium proliferative activity level of stromal cells [the median of Ki-67 expression level in adenomas was 2,94% (1,23; 4,35), in hyperplastic polyps – 1,18% (1,10; 1,86), ($p<0,05$)].

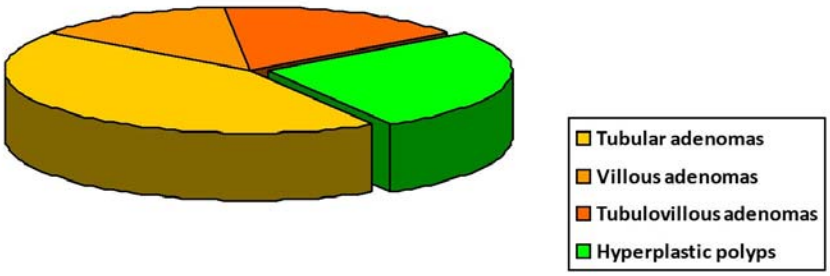

Fig. 1. The ratio of the different histological types of adenomas and hyperplastic polyps in the researched material.

The direct strong relation between the medium Ki-67 expression level by epitheliocytes and the low Ki-67 expression level by stromal cells was revealed using Spearman's rank correlation coefficient: r=0,75 for adenomas, r=0,83 for hyperplastic polyps.

The analysis of proliferation activity levels of adenomas' cells depending on the grade of dysplasia was also done: the median of Ki-67 expression level by epitheliocytes in adenomas with low-grade dysplasia was 49,19% (43,08; 65,39), in adenomas with high-grade dysplasia – 76,23% (62,36; 85,36), ($p<0,05$); the median of Ki-67 expression level by stromal cells in adenomas with low-grade dysplasia was 1,35% (1,12; 2,81), in adenomas with high-grade dysplasia – 4,12% (3,07; 6,29), ($p<0,05$). The difference between the figures that were obtained for hyperplastic polyps (without dysplasia), adenomas with low-grade dysplasia, and adenomas with high-grade dysplasia was statistically significant. These data are shown in the Fig. 2.

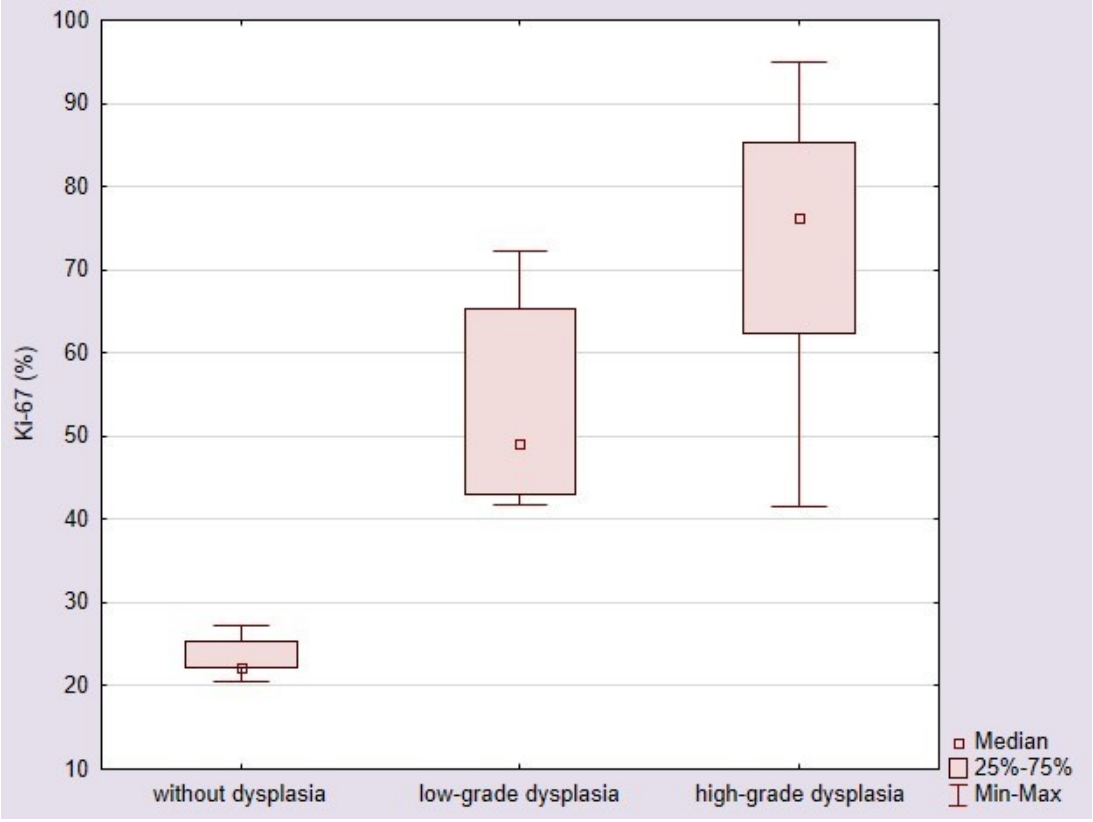

Fig. 2. The medians of Ki-67 expression by epitheliocytes of distal colonic polyps without dysplasia, with low-grade dysplasia, and with high-grade dysplasia.

Moreover, the direct medium relation between the medium Ki-67 expression level by adenomas' epitheliocytes and the grade of dysplasia (γ=0,65) was revealed as well as the direct strong relation between the low Ki-67 expression level by adenomas' stromal cells and the grade of dysplasia (γ=0,70).

According to the results of IHC study of p53 oncoprotein it was revealed that the DCP are characterized by the low p53 expression level by epithelial and stromal cells: the median of p53 expression by epitheliocytes of adenomas was 2,39% (1,58; 8,26), by epitheliocytes of hyperplastic polyps – 0,00% (0,00; 1,47), (p<0,05); the median of p53 expression by stromal cells of adenomas was 1,23% (0,72; 1,49), by stromal cells of hyperplastic polyps was 0,00% (0,00; 0,05), (p<0,05).

According to the results of correlation analysis the direct medium relation between the low levels of p53 expression by epitheliocytes and stromal cells of adenomas (r=0,59), and also the direct strong relation between the low levels of p53 expression by epitheliocytes and stromal cells of hyperplastic polyps (r=0,90) were revealed. Furthermore, there is the statistically significant difference between the p53 expression levels by epitheliocytes of adenomas of different histological types: the median of p53 expression level in tubular adenomas was 2,35% (1,53;5,62), in tubulovillous adenomas – 1,73% (1,68; 2,02), and in villous adenomas – 8,71% (8,40; 9,02), (p<0,05).

The results of comparative analysis of p53 expression level depending on the grade of dysplasia: the median of p53 expression level by epitheliocytes of adenomas with low-grade dysplasia was 1,86% (1,39; 5,25), by epitheliocytes of adenomas with high-grade dysplasia was 8,26% (1,73; 9,15), (p<0,05); the median of p53 expression level by stromal cells of adenomas with low-grade dysplasia was 0,93% (0,25; 1,63), by stromal cells of adenomas with high-grade dysplasia was ,29% (0,72; 1,49), (p<0,05). The difference that was obtained for hyperplastic polyps (without dysplasia), adenomas with low-grade dysplasia, and adenomas with high-grade dysplasia was statistically significant. These data are shown in the Fig. 3. Moreover, there is a direct medium correlation between the low 53 expression level by epitheliocytes of adenomas and the grade of dysplasia (γ=0,53).

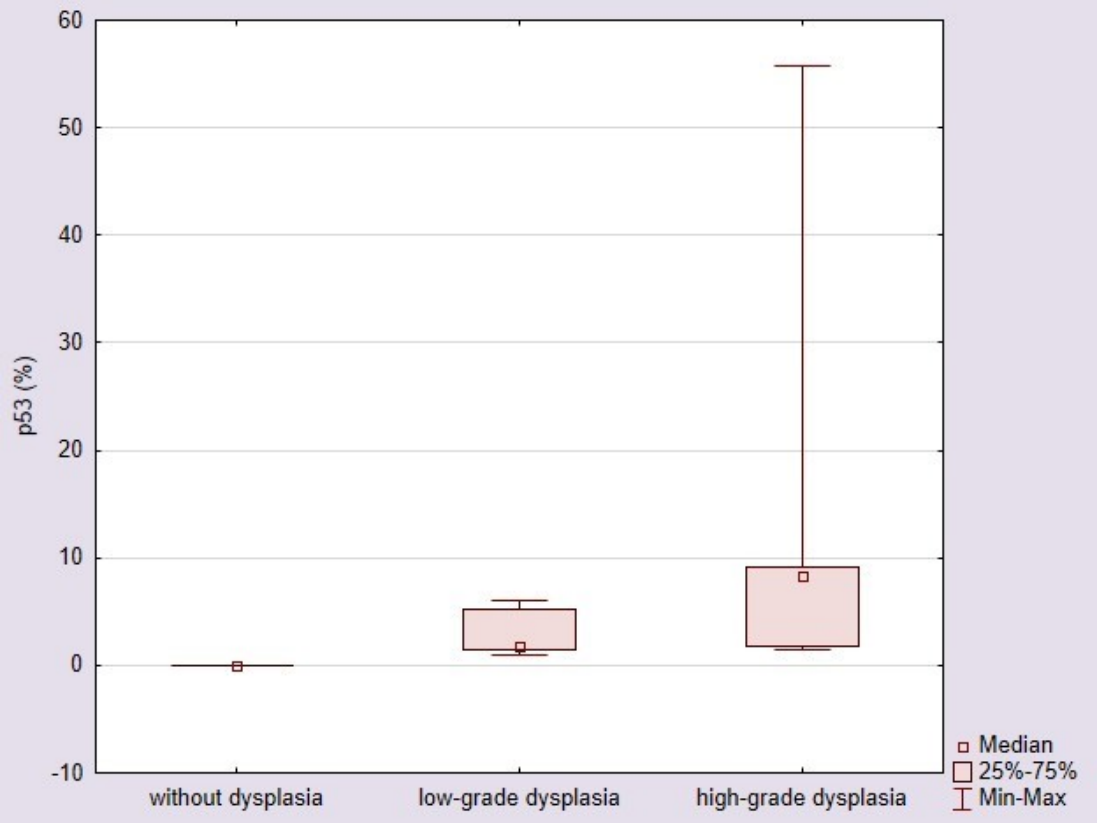

Fig. 3. The medians of p53 expression by epitheliocytes of distal colonic polyps without dysplasia, with low-grade dysplasia, and with high-grade dysplasia.

According to the results of IHC study of caspase-3 (the marker of apoptotic degradation) it was established that the DCP are characterized by the low apoptosis level of epithelial and stromal cells: the median of caspase-3 expression by adenomas' epitheliocytes was 31,84 CUOD (19,53; 42,34), by

hyperplastic polyps' epitheliocytes – 16,99 CUOD (11,86; 39,85), (p>0,05); the median of caspase-3 expression by adenomas' stromal cells was 43,87 CUOD (25,47; 73,09), by hyperplastic polyps' stromal cells – 28,64 CUOD (19,20; 30,71), (p<0,05).

According to the results of correlation analysis the direct strong relation between the low caspase-3 expression levels by epithelial and stromal cells (r=0,92). Moreover, the statistically significant differences between caspase-3 expression levels by epithelial and stromal cells of adenomas of different types: the median of caspase-3 expression by epitheliocytes of tubular adenomas was 20,38 CUOD (18,08; 26,53), of tubulovillous adenomas – 33,78 CUOD (32,15; 40,25), of villous adenomas –67,88 CUOD (63,92; 71,29), (p<0,05); the median of caspase-3 expression by stromal cells of tubular adenomas was 27,44 CUOD (22,19; 33,48), of tubulovillous adenomas – 52,26 CUOD (51,70; 55,26), of villous adenomas –88,72 CUOD (85,69; 92,13), (p<0,05).

The analysis of apoptosis levels of adenomas' cells depending on the grade of dysplasia was also done: the median of caspase-3 expression by epitheliocytes of adenomas with low-grade dysplasia was 20,38 CUOD (18,08; 26,52), with high-grade dysplasia – 42,34 CUOD (33,78; 65,38), (p<0,05); the median of caspase-3 expression by stromal cells of adenomas with low-grade dysplasia was 27,44 CUOD (22,19; 33,48), with high-grade dysplasia – 55,26 CUOD (49,17; 86,20), (p<0,05). The difference that was obtained for hyperplastic polyps, adenomas with low-grade dysplasia, and adenomas with high-grade dysplasia was statistically significant. These data are shown in the Fig. 4. Moreover, the direct strong relation between the low caspase-3 expression level by adenomas' epitheliocytes and the grade of dysplasia (γ=0,80) as well as the direct medium relation between the low caspase-3 expression level by adenomas' stromal cells and the grade of dysplasia (γ=0,63) were revealed.

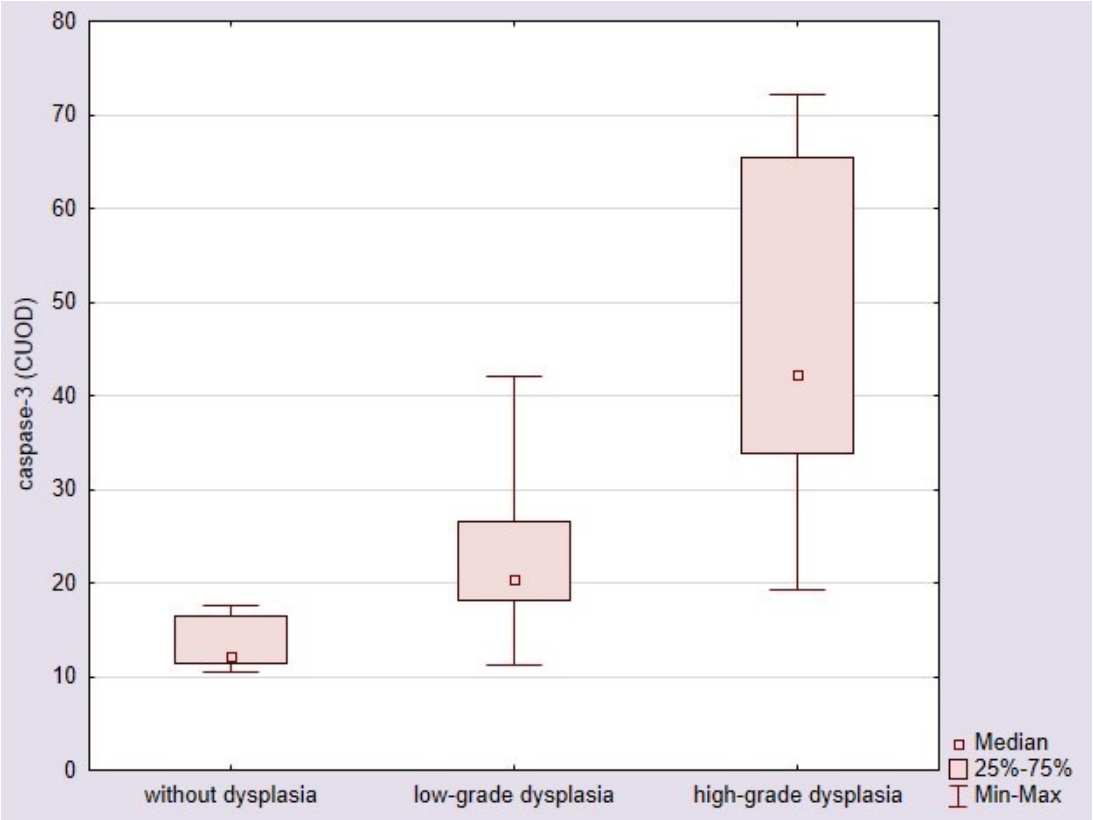

Fig. 4. The medians of caspase-3 expression by epitheliocytes of distal colonic polyps without dysplasia, with low-grade dysplasia, and with high-grade dysplasia.

The correlations between proliferation and apoptosis levels in the DCP were studied as well. The direct strong relation between the medium level of proliferation of epitheliocytes and the low level of p53 accumulation in their nuclei (r=0,71 for adenomas and r=0,79 for hyperplastic polyps) as well as the direct medium relation between the medium level of proliferation of adenomas' epitheliocytes and the low level of their apoptosis (r=0,61) were revealed. Furthermore, the direct medium relation between the low level of p53 accumulation by adenomas' epitheliocytes and the low level of their apoptosis (r=0,59) as well as the direct strong relation between the low level of p53 accumulation by hyperplastic polyp's epitheliocytes the low level of their apoptosis (r=0,79) were revealed.

According to the current literature dysplasia is an obligatory characteristic of adenomas [5], that is consistent with the results of this study: 56% of researched adenomas had low-grade dysplasia, 44% – high-grade dysplasia. It's also known that dysplastic changes of epithelium are not typical of hyperplastic polyps [5]. There weren't any dysplastic changes among the hyperplastic polyps that were studied. Moreover, it's well known that serrated polyps are characterized by the specific tendency of localization: traditional serrated adenomas and sessile serrated adenomas are located mainly in the proximal colon, whereas hyperplastic polyps are located mainly in the distal colon [1,3]. The researched DCP were presented by hyperplastic polyps that is concordant with the literature data.

The medium proliferation level of epitheliocytes in colonic polyps was described in the current literature [14,15], while the question of the proliferation level of stromal cells in these polyps wasn't studied. The low proliferation level of the DCP' stromal cells was established in this study. Furthermore, the direct strong correlation between the medium proliferation level of epitheliocytes and the low proliferation level of stromal cells was revealed (r=0,75 in adenomas and r=0,83 in hyperplastic polyps) which indicates a close association between the proliferation activity of epithelial and stromal cells.

The correlations between the Ki-67 expression level and the dysplasia grade in adenomas that were revealed in this study (γ=0,65 for epitheliocytes and γ=0,70 for stromal cells) consider a priority of increased proliferation in progression of dysplastic changes. It's noteworthy that association between the proliferation level of stromal cells and the dysplasia grade is even more prominent than the association between the proliferation level of epitheliocytes and the dysplasia grade that highlight the essential role of this cells in DCP progression. According to the literature data an increased proliferation that happens during the adenoma's progression is mediated by *APC* gene mutations in 70% cases [15]. These mutations lead to permanent activation of the Wnt/β-catenin signaling pathway resulting in increased inflammatory cytokine production, abnormal apoptosis, undesirable epithelial cell proliferation/differentiation, and epithelial cell transformation [16].

The data about p53 expression features in the DCP that were obtained in this study are also concordant with the literature data [14,15,17]. Moreover, it was revealed that there are statistically significant differences between the p53 expression levels in adenomas of different histological types. The pronounced tendency of epitheliocytes of villous adenomas to accumulate the p53 oncoprotein consistent with the well-established idea about the greatest malignant potential of villous adenomas in comparison with tubular and tubulovillous adenomas [5].

The correlations that was revealed between the p53 expression levels and the dysplasia grade in adenomas' cells indicate the close association between accumulation of p53 oncoprotein in nuclei and dysplastic changes in cells. According to X. Sui et al. (2015) the p53 oncoprotein which is found in immunostained slides doesn't perform the tumor-supressor function but does promote cell proliferation and invasion of atypical epitheliocytes [18].

It was revealed that the cells of DCP are characterized by the low caspase-3 expression level. R.B. Nogueira et al. (2013) reported about the medium caspase-3 expression level but the researchers studied the caspase-3 expression in all kind of polyps' cells without separation into epithelial cells and stromal cells [17].

The correlations between caspase-3 expression level and the dysplasia grade in adenomas that were revealed in this study (γ=0,80 for epitheliocytes and γ=0,63 for stromal cells) indicate the association between progression of dysplastic polyps and activation of apoptosis of their cells. Noteworthy that the association between the apoptotic activity of epitheliocytes and the dysplasia grade is even more prominent than the association between the apoptotic activity of stromal cells and the dysplasia grade that highlight the essential role of these cells in the DCP progression. There is the information about increasing of apoptosis in colonic polyps in their progression [19] as well as the information about decreasing of apoptosis in colonic polyps in their progression [9,10]. The correlations that were revealed in this study might be explained by a preservation of compensatory mechanisms of apoptotic death of epithelial cells during their atypical transformation at the low-grade and high-grade dysplasia in a polyp.

The correlations that were revealed between the expression levels of proliferation and apoptosis markers indicate the close association between the processes of cell proliferation, p53 oncoprotein accumulation, and apoptosis in the DCP. According to the literature data the molecular basis for these correlations might be formed from signaling pathways (Wnt/β-catenin signaling, MAPK, CIN) that involved in the regulation of epithelial cell proliferation and apoptosis [2,16,18]. However, the deeper understanding of functioning and role of those signaling pathways during malignant transformation process in the distal colon requires further molecular-genetic studies.

Conclusions

1. Distal colonic polyps are characterized by the medium level of proliferative activity of epithelial cells [Me = 62.40% (48.65; 76.23) in adenomas, Me = 26.23% (22.19; 48.88) in hyperplastic polyps] and the low level of proliferative activity of stromal cells [Me = 2.94% (1.23; 4.35) in adenomas, Me = 1.18% (1.10; 1.86) in hyperplastic polyps], that were evaluated by the Ki-67 immunohistochemical expression.

2. The low level of p53 oncoprotein expression is typical of the distal colonic polyps' cells: Me = 2.39% (1.58; 8.26) for epithelial cells of adenomas, Me = 1.23% (0.72; 1.49) for stromal cells of adenomas, Me = 0.00% (0.00; 1.47) for epithelial cells of hyperplastic polyps, and Me = 0.00% (0.00; 0.05) for stromal cells of hyperplastic polyps.

3. Distal colonic polyps are characterized by the low level of apoptosis of epitheliocytes [Me=31,84CUOD (19,53; 42,34) in adenomas, Me=16,99CUOD (11,86; 39,85) in hyperplastic polyps] and stromal cells [Me=43,87CUOD (25,47; 73,09) in adenomas, Me=28,64CUOD (19,20; 30,71) in hyperplastic polyps], that were evaluated by the caspase-3 immunohistochemical expression.

4. There are correlations between the expression levels of the proliferation and apoptosis markers, and the dysplasia grade: between the average Ki-67 expression level by epithelial cells and the grade of dysplasia (γ=0.65), between the low Ki-67 expression level by stromal cells and the grade of dysplasia (γ=0.70), between the low p53 expression level by epithelial cells and the grade of dysplasia (γ=0.53), between the low caspase-3 expression level by epithelial cells and the grade of dysplasia (γ=0.80), as well as between the low caspase-3 expression level by stromal cells and the grade of dysplasia (γ=0.63).

5. The proliferation and apoptosis levels in distal colonic polyps correlate: there is the correlation between the Ki-67 and p53 expression levels (r=0.71 in adenomas, r=0.79 in hyperplastic polyps), the correlation between the Ki-67 and caspase-3 expression levels in adenomas (r=0.61), the correlation between the p53 and caspase-3 expression levels (r=0.59 in adenomas, r=0.79 in hyperplastic polyps).

Information about conflicts of interest

Potential or explicit conflicts of interest related to this manuscript do not exist and are not foreseen at the time of publication.

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Шишкін М. А., Христенко Т. О. Поліпи дистальних відділів товстої кишки: імуногістохімічна характеристика проліферації та апоптозу.

РЕФЕРАТ. Актуальність. Добре відомо, що поліпи кишківника можуть буди попередниками колоректального раку. Однак, точні імуногістохімічні параметри, зокрема рівні проліферації та апоптозу клітин поліпів, що можуть буди прогностично значущими, досі на встановлені. **Мета**. Вивчити особливості імуногістохімічної експресії маркерів проліферації та апоптозу в поліпах дистальних відділів товстої кишки. **Методи.** Проведено патоморфологічне та імуногістохімічне дослідження біопсій поліпів дистальних відділів товстої кишки 30 пацієнтів 41-83 років, що пройшли ендоскопічне обстеження в УКЗДМУ в 2016 році. **Результати.** Поліпи дистальних відділів товстої кишки характеризуються середнім рівнем проліферативної активності епітеліоцитів [Me=62,40% (48,65; 76,23) для аденом, Me=26,23% (22,19; 48,88) для гіперпластичних поліпів], низьким рівнем проліферативної активності клітин строми [Me=2,94% (1,23; 4,35) для аденом, Me=1,18% (1,10; 1,86) для гіперпластичних поліпів], низьким рівнем експресії маркеру мутантного білка p53 епітеліоцитами і клітинами строми [Me=2,39% (1,58; 8,26) і Me=1,23% (0,72; 1,49) для клітин аденом, Me=0,00% (0,00; 1,47) і Me=0,00% (0,00; 0,05) для клітин гіперпластичних поліпів], а також низьким рівнем апоптотичної активності епітеліоцитів і клітин строми [Me=31,84УООГ (19,53; 42,34) і Me=43,87 УООГ (25,47; 73,09) для аденом, Me=16,99 УООГ (11,86; 39,85) і Me=28,64 УООГ (19,20; 30,71) для гіперпластичних поліпів]. Існують кореляції між характерними рівнями експресії маркерів проліферації, апоптозу та ступенем тяжкості дисплазії аденом дистальних відділів товстої кишки: між рівнями експресії Ki-67 клітинами епітелію і строми, а також ступенем дисплазії (γ=0,65 і γ=0,70, відповідно); між рівнем експресії p53 епітеліоцитами і ступенем дисплазії (γ=0,53); між рівнями експресії каспази-3 клітинами епітелію і строми, а також ступенем дисплазії (γ=0,80 і γ=0,63, відповідно). Окрім того, характерні для поліпів дистальних відділів товстої кишки показники рівнів експресії маркерів проліферації і апоптозу епітеліоцитів корелюють: існує зв'язок між рівнями експресії Ki-67 і p53 (r=0,71 для аденом, r=0,79 для гіперпластичних поліпів), рівнями експресії Ki-67 і каспази-3 (r=0,61 для аденом), між рівнями експресії p53 і каспази-3 (r=0,59 для аденом, r=0,79 для гіперпластичних поліпів). **Підсумок.** Отримані данні свідчать про наявність асоціативного зв'язку між процесами клітинної проліферації, накопичення мутантного протеїну p53, а також апоптотичної загибелі клітин поліпів дистальних відділів товстої кишки.

Ключові слова: поліпи, товстий кишечник, проліферація, апоптоз, онкосупресорний протеїн p53, каспаза-3.

Шишкин М. А., Христенко Т. А. Полипы дистальных отделов толстого кишечника: иммуногистохимическая характеристика пролиферации и апоптоза.

РЕФЕРАТ. Актуальность. Известно, что полипы кишечника могут быть предшественниками колоректального рака. Однако, точные иммунгистохимические параметры, в частности уровни пролиферации и апоптоза клеток полипов, которые могут быть прогностически значимы, до сих пор не установлены. **Цель**. Изучить особенности иммуногистохимической экспрессии маркеров пролиферации и апоптоза в полипах дистальных отделов толстого кишечника. **Методы.** Проведено патоморфологическое и иммуногистохимическое исследование биопсий полипов дистальных отделов толстого кишечника 30 пациентов 41-83 лет, прошедших эндоскопическое обследование в УКЗГМУ в 2016 году. **Результаты.** Полипы дистальных отделов толстого кишечника характеризуются средним уровнем пролиферативной активности эпителиоцитов [Me=62,40% (48,65; 76,23) для аденом, Me=26,23% (22,19; 48,88) для гиперпластических полипов], низким уровнем пролиферативной активности клеток стромы [Me=2,94% (1,23; 4,35) для аденом, Me=1,18% (1,10; 1,86) для гиперпластических полипов], низким уровнем экспрессии маркера мутантного белка p53 эпителиоцитами и клетками стромы [Me=2,39% (1,58; 8,26) и Me=1,23% (0,72;

1,49) для клеток аденом, Me=0,00% (0,00; 1,47) и Me=0,00% (0,00; 0,05) для клеток гиперпластических полипов], а также низким уровнем апоптотической активности эпителиоцитов и клеток стромы [Me=31,84УЕОП (19,53; 42,34) и Me=43,87УЕОП (25,47; 73,09) для аденом, Me=16,99УЕОП (11,86; 39,85) и Me=28,64УЕОП (19,20; 30,71) для гиперпластических полипов]. Существуют корреляции между характерными уровнями экспрессии маркеров пролиферации, апоптоза и степенью тяжести дисплазии аденом дистальных отделов толстого кишечника: между уровнями экспрессии Ki-67 клетками эпителия и стромы, а также степенью дисплазии (γ=0,65 и γ=0,70, соответственно); между уровнем экспрессии p53 эпителиоцитами и степенью дисплазии (γ=0,53); между уровнями экспрессии каспазы-3 клетками эпителия и стромы, а также степенью дисплазии (γ=0,80 и γ=0,63, соответственно). Кроме того, характерные для полипов дистальных отделов толстого кишечника показатели уровней экспрессии маркеров пролиферации и апоптоза эпителиоцитами коррелируют: существует связь между уровнями экспрессии Ki-67 и p53 (r=0,71 для аденом, r=0,79 для гиперпластических полипов), уровнями экспрессии Ki-67 и каспазы-3 (r=0,61 для аденом), между уровнями экспрессии p53 и каспазы-3 (r=0,59 для аденом, r=0,79 для гиперпластических полипов). **Заключение.** Полученные данные свидетельствуют о наличии тесной ассоциации между процессами клеточной пролиферации, накопления мутантного белка p53, а также апоптотической гибели клеток полипов дистальных отделов толстого кишечника.

Ключевые слова: полипы, толстый кишечник, пролиферация, апоптоз, онкосупрессорный протеин p53, каспаза-3.