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IMPORTANCE OF SEROUS INTRAEPITHELIAL OVARIAN TUBAL CARCINOMAS IN THE OCCURRENCE OF "HIGH-GRADE" SEROUS CARCINOMAS AND / OR PERITONEAL SEROUS CARCINOMAS OF UNKNOWN PRIMARY ORIGIN

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Ключевые слова: *"high-grade" серозные карциномы яичников, раки без известной первичной локализации, p53, ImageJ*

Abstract. Importance of serous intraepithelial ovarian tubal carcinomas in the occurrence of "high-grade" serous carcinomas and / or peritoneal serous carcinomas of unknown primary origin. Shponka I.S., Poslavska O.V., Savchenko O.A. *Studies of the recent decades on serous pelvic adenocarcinomas in women have set the goal of distinguishing between two diagnostic units: "low-grade" and "high-grade" carcinomas. The precursors of the "low-grade" variant (type I) is considered to be a borderline serous tumor / atypical proliferative serous tumor (8442/1), which according to the International Classification of Diseases for Oncology ICD-O 2013 of the female reproductive system refers to non-specific, borderline tumors and tumors with unpredictable clinical behavior. The precursors of the “high-grade” variant (type II) are serous tubular intraepithelial carcinomas (in situ) or “high-grade” serous invasive tubal carcinomas, since they have the TP53 mutation identical to “high-grade” ovarian carcinoma, an*

aberrant p53 protein expression, high proliferative activity, and significant genomic instability. In addition, according to the carcinogenesis of "high-grade" serous ovarian carcinoma with metastases to the peritoneum, it can also be interpreted as "pelvic high-grade serous carcinoma". A retrospective analysis of the histological, morphometric and immunohistochemical characteristics of the biopsy material of 31 women aged from 28 to 76 years (mean 57.32±11.54; median 57), divided into 3 groups, was carried out. Group 1: 14 observations of the tubal epithelium (8 tubes without pathological changes (subgroup 1a) and 6 with signs of intraepithelial neoplasia (subgroup 1b); group 2: 12 cases of serous adenocarcinoma of the ovary of the "high-grade" variant; group 3: 6 metastatic peritoneal serous carcinoma with unknown primary site. Results. Group immunophenotypes showed uniformity in the expression of markers CK7 (+, +/-), CK20 (-), WT-1 (+), CA125 (+, +/-), with an affinity to distal uterine tube fragments. The expression of p53 in all groups with signs of carcinomas (compared with the control subgroup 1a without atypia) was divided into two options - negative samples and samples with overexpression, where no statistically significant difference was found (p>0.05), which is possibly a single way of carcinogenesis. The morphometric study revealed a significant difference in the area of the nuclei between group 3 and the first three groups (1a, 1b, 2), which indicates the similarity of ovarian and tubal neoplasias and uterine tube epithelium. The number of intranuclear reactions with ER and PGR progressively decreased from group 1 to group 3, with an increase in cases with ER (+/-) / PGR (+/- or -) to 50% in group 3, which greatly complicated the diagnostic search for unknown carcinomas of primary localization. HER-2-new expression revealed a possible amplification (gradation 2 + / 3 +) only in group 2 at the level of 16.67% and in group 3 at the level of 33.33%.

Реферат. Значение серозных интраэпителиальных карцином маточных труб в возникновении "high-grade" серозных карцином яичников и / или перитонеальных серозных карцином неизвестной первичной локализации. Шпонька И.С., Пославская А.В., Савченко О.А. *Исследования последних десятилетий серозных аденокарцином малого таза женщин ставили перед собой цель различить две диагностические единицы: "low-grade" и "high-grade" карцином. Предшественником "low-grade" варианта (тип I) считается пограничная серозная опухоль / атипичная пролиферирующая серозная опухоль (serous borderline tumor / atypical proliferative serous tumor - 8442/1), что по Международной классификации онкологических болезней (International Classification of Diseases for Oncology ICD- O 2013) репродуктивной системы женщин относится к неспецифическим, пограничным опухолям и опухолям с непредсказуемым клиническим поведением. Предшественниками "high-grade" варианта (тип II) рассматриваются серозные тубулярные интраэпителиальные карциномы (in situ) или "high-grade" серозные инвазивные карциномы маточных труб, так как они имеют идентичные для "high-grade" серозной карциномы яичников мутацию TP53, аберрантную экспрессию протеина p53, высокую пролиферативную активность и значительную геномную нестабильность. К тому же, согласно канцерогенезу "high-grade" серозной карциномы яичника с метастазами в брюшину, она также может быть трактована как "pelvic high-grade serous carcinoma". В работе проведен ретроспективный анализ гистологических, морфометрических и иммуногистохимических характеристик биопсийного материала 31 женщины от 28 до 76 лет (среднее 57,32±11,54; медиана 57), распределенного на 3 группы. Группа 1: 14 наблюдений эпителия маточных труб (8 труб без патологических изменений (подгруппа 1а) и 6 с признаками интраэпителиальной неоплазии (подгруппа 1б); группа 2: 12 случаев серозных аденокарцином яичника варианта "high-grade"; группа 3: 6 метастатических перитонеальных карцином серозного типа без известного первичного источника. Иммунофенотипы групп показали однородность в экспрессии маркеров CK7 (+, +/-), CK20 (-), WT-1 (+), CA125 (+, +/-), со сродством к дистальным фрагментам маточных труб. Экспрессия p53 во всех группах с признаками карцином (по сравнению с контрольной подгруппой 1а без атипии) разделилась на два варианта - отрицательные образцы и образцы со сверхэкспрессией, где среди средних значений p53 статистически достоверной разницы обнаружено не было (p>0,05), что, возможно, является единным путём канцерогенеза. Морфометрическое исследование выявило достоверную разницу в показателях площади ядер между группой 3 и всеми первыми тремя группами (1а, 1б, 2), что говорит о сходстве яичниковых и трубных неоплазий и эпителия маточной трубы. Количество интрануклеарних реакций с ER и PGR прогрессивно уменьшалось от группы 1 к группе 3, с увеличением случаев с ER (+/-) / PGR (+/- или -) до 50% в группе 3, что значительно осложняло диагностический поиск для карцином неизвестной первичной локализации. Экспрессия HER-2-new обнаружила возможную амплификацию (градации 2 + / 3 +) только в группе 2 на уровне 16,67% и в группе 3 на уровне 33,33%.*

Statistically, most metastatic serous carcinomas in women have an association with the ovaries, it has long been believed that they are primary and appear in the ovaries with a further rapid spread in the abdominal cavity [8]. But recent studies of serous adenocarcinoma (AC) of the female pelvis have set the goal of distinguishing two diagnostic units: "low-grade" and "high-grade" carcinoma. Thus, a dualistic model of the origin of ovarian epithelial tumors was developed, with the distribution of serous carcinomas into 2 categories: type I and type II [8, 10, 14]. According to the literature, type I is a "low-grade" serous ovarian adenocarcinoma (OAC) containing a high frequency of KRAS and / or BRAF gene mutations but no TP53 oncogene suppressor mutations [8, 13, 14]. In turn,

type II, which accordingly has a high-grade analogue of serous carcinoma, is characterized by a high level of genetic instability with the involvement of the TP53 mutation. Different ways of carcinogenesis of these two types of serous ovarian carcinomas are likely to occur [3, 13, 18].

The precursor of the "low-grade" variant is the serous borderline tumor / atypical proliferative serous tumor (8442/1), which according to the International Classification of Diseases for Oncology ICD-O 2013) of female reproductive.system is related to the non-specific, borderline tumors and tumors with unpredictable clinical behavior [5, 8, 15]. A non-invasive serous tumor exhibits a sufficient number of micropapillary patterns and is more commonly associated with a synchronous and / or metasynchronous invasive process. Evidence for this is that *serous borderline tumor / atypical proliferating serous tumor* and "low-grade" serous AC have similar KRAS and / or BRAF gene mutations and small chromosomal abnormalities [9, 11, 17].

Unlike the previous type, "high-grade" serous carcinoma (type II) shows a TP53 mutation and genetic instability. According to statistics, this aggressive process is often diagnosed in the common state. Although the "low-grade" serous variant of cancer can rarely progress to "high-grade", most of them develop in their own way [4, 5].

Thus, according to the carcinogenesis of "high-grade" serous ovarian carcinoma with metastases to the peritoneum, it can be interpreted as "pelvic high-grade serous carcinomas" and, according to the latest recommendations, all the above-mentioned localization of detection of "high-grade" serous AC are combined because of the inability to identify the main primary source or the assumption of their origin from the tubal intraepithelial neoplasia [5].

The aim of the work was to compare histological, morphometric and immunohistological characteristics of the tube epithelium with signs of intraepithelial neoplasia, high-grade ovarian adenocarcinoma and non-primary metastatic peritoneal carcinoma for detection of a possible affinity of their phenotypes.

MATERIALS AND METHODS OF RESEARCH

A retrospective analysis of histological, immunohistological and morphometric characteristics of biopsy and postoperative material of 31 women aged from 28 to 76 years (mean 57.32±11.54; median 57) divided into three groups was made. *Group 1:* 14 observations of the uterine tube epithelium (8 tubes without abnormal changes (subgroup 1a) and 6 - with signs of intraepithelial neoplasia (subgroup 1b); *group 2:* 12 cases of high-grade serous ovarian adenocarcinomas (10 of them had examined uterine tubes from group 1); *group 3:* 6 metastatic peritoneal AC of serous type without known primary source. Blocks and glasses of the studied material were taken from the archives of the oncology department and the department of general pathology of MI "Dnipropetrovsk regional pathological and anatomical bureau", Dnipro, over the period of 2015-2018.

For the morphometric method a Zeiss Primo Star – Axiocam ERC 5s microscope camera with ZEN 2 blue edition licensed software was used, the information fields of view were recorded in jpg format and processed in Imagej software to determine the perimeter, area and circularity of nuclei and the nuclear reaction according to the method described in previous publications [1, 2]. Immunohistochemical study was performed according to the protocols of the company TermoScientific (TS), (USA) on the basis of morphological department of the medical-diagnostic center of LLC "Pharmacies of Medical Academy" (Dnipro) for the period of 2015-2018. In the specimens thicker than 4 mcm, visualization system Lab Vision Quanto (TS, USA) was used, with protein chain detection by DAB Quanto Chromogen (TS, USA). The characteristics of the monoclonal antibodies that were used are listed in table 1.

Evaluation of the p53 marker was performed by criterion of 5%, namely: intranuclear p53 expression less than 5% was considered negative, in the range of 5-60% – "normal", 60% and more in the form of "blocks" – overexpression [5, 7]. The positive reactions of the Her-2-new marker on the cell membrane were evaluated by a scale developed for cases with amplification of the Her-2 gene, where 0 and 1+ (up to 10% and more than 10% of cells, respectively, with weak staining), without amplifications, and 2+ and 3+ (more than 10% of cells with moderate and intense membrane staining, respectively) are likely to have amplification of this gene. Evaluation of intranuclear reactions WT-1, ER, PGR was estimated as the percentage of positively stained brown nuclei per 100 cells at 400 of magnification.

Statistical analysis of the data was performed in Microsoft Excel with the calculation of minimum, maximum, median, arithmetic and standard deviation. The statistical significance of differences in the number of observations in groups was verified using the Fisher test, the statistical significance of differences in the mean values was tested using the t criterion in R version 3.4.1 (2017-06-30) – "Single Candle" Copyright (C) 2017 ; The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32 / x64 (64-bit). A p value <0.05 was considered statistically significant [2].

Table 1

Primary mononuclear antibodies

Primary antibodies	Clon (dilution)	Localization of reaction
CA125	Ab-1 (1:10)	Membrane
Cytokeratin 7 (CK7)	RCK105 (1:100)	Cytoplasm
Cytokeratin 20 (CK20)	Ks 20.8 (1:100)	Cytoplasm
WT-1	Ab-1 (1:500)	Nucleus
ER	Ab-1/sp-1 (1:200)	Nucleus
PGR	YR85 (1:200)	Nucleus
p53	Ab-3 (1:100)	Nucleus
HER-2/neu	Ab-1 (1:100)	Membrane

RESULTS AND DISCUSSION

When comparing the immunophenotypes of the study groups, it was found that the ratio of diagnostic cytokeratins Cytokeratin 7 (CK7) and Sytokeratin 20 (CK20) was quite the same for all cases: CK7 (+ or +/-) but CK20 was strictly (-) (Fig. 1 a, b, c). The inhomogeneous decrease in CK7 expression, which was regarded as (+/-), was found in *subgroup 1a* (up to 53% of cells) of distal fragments of 3 FT observations (unstained goblet cells, as well as partially light tubular type epithelial cells), *in group 2* of serous tubular type “high-grade” OAC (up to 62% of cells) and in *group 3* of metastatic peritoneal AC of serous type without known primary source (up to 59% of cells).

Regarding serous OAC marker WT-1 (Fig. 1 d, e, f), it should be noted that its positive status was selected as a criterion for the selection of cases in *groups 2 and 3*, and was therefore thoroughly investigated in *subgroups 1a and b* as probable sources origin. There was a difference in the expression of WT-1 in the distal and proximal regions of the FT with the predominance of the percentage of positive intranuclear reactions in the distal regions. It should be noted that 3 tubes from 8 (37.5%) of *subgroup 1a* and 2 tubes from 6 (33.33%) of *subgroup 1b* had negative WT-1 reactions in the distal and proximal fragments.

Diagnostic mucin type 16, known as CA125 and inherent to OAC, also had heterogeneous membrane staining in *subgroups 1a and b* of FT fragments with reduced number of stained cells in proximal fragments, sometimes until complete disappearance (3 cases), and in *group 3* – metastatic peritoneal carcinomas is a fragmentary membrane staining of papillary structures, but in *group 2* OAC expression of CA 125 was stable (+) (Fig. 1 g, h, i).

The prognostic marker p53 was also investigated (Fig. 1 j, k, l), which was determined to obtain data on the mutation of the TP53 gene due to the presence of aberrant expression (above 60% – overexpression, or below 5% – lack of expression) and was considered as pathway of carcinogenesis of serous tumors of "high-grade" type [5, 6, 11]. Expression rates of p53 observations of uterine tubes of *subgroup 1a* (without atypia), which ranged from 7.04±1.26 among their proximal and distal fragments, were taken as normal.

Expression of p53 in *subgroup 1b* (intraepithelial neoplasia of fallopian tube) was found in two variants – negative samples 4 out of 6 (66.67%) (<5% stained cells) and overexpression in 2 out of 6 (33.33%), fluctuations within 67.78±13.51, with quantitative predominance in distal fragments (fimbriae) (Fig. 1 j). Expression of p53 in *group 2* among serous OAC also had a distribution into negative samples: 5 out of 12 (41.67%) and samples with overexpression 7 out of 12 (58.33%), fluctuations within 73.24±8.93 (Fig. 1 k). Expression of p53 in *group 3* among metastatic peritoneal carcinomas of serous type witht unknown primary source, respectively, showed negative samples: 4 out of 6 (66.67%) and samples with overexpression 2 out of 6 (33.33%), where fluctuations were within 65.93±4.74 (Fig. 1 l). No statistically significant difference between p53 overexpression was found in the study groups (p>0.05).

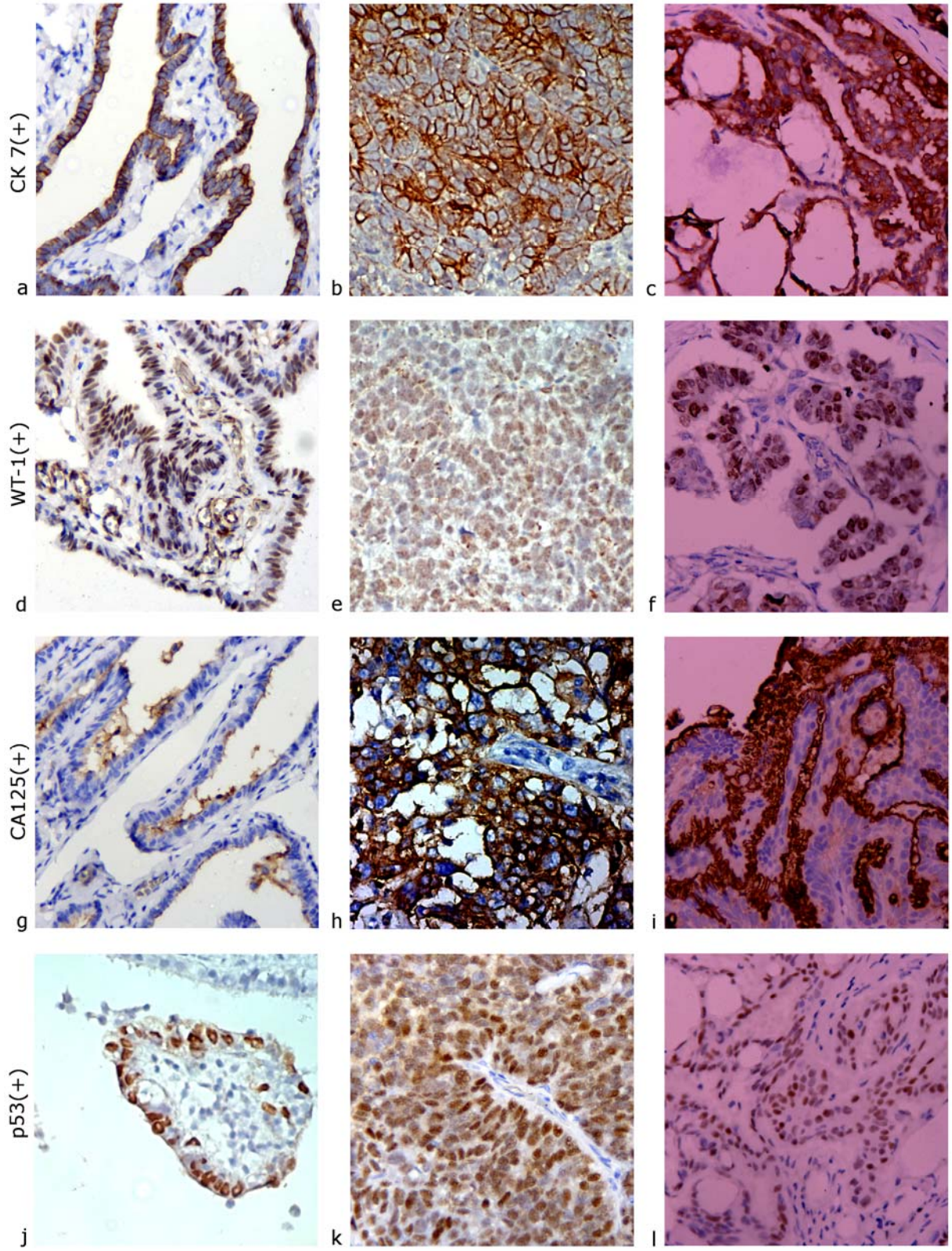

Fig. 1. Immunohistochemical research, (×400). Epithelium of fallopian tube with signs of intraepithelial neoplasia (a, d, g, j). Serous "high-grade" ovarian adenocarcinoma (OAC) (b, e, h, k). Metastatic serous peritoneal carcinoma without known primary site (c, f, i, l). Cytoplasmic reaction with CK7 (a, b, c). Intranuclear expression of WT-1 (d, e, f). Membrane expression of CA 125 (g, h, i). Intranuclear expression of p53 (j, k, l)

The micrographs of specimens of the studied groups were also subjected to morphometric analysis in the ImageJ program, with the determining areas, perimeters and the "circularity" of their nuclei to confirm their similarity (Table 2).

Table 2

Findings of morphometric examination of fallopian tube epithelium without and with signs of intraepithelial neoplasia, "high-grade" ovarian adenocarcinoma and metastatic serous peritoneal carcinoma with unknown primary site in ImageJ, χ±SD

Type of tumor	n	Area (mkm^2) χ±SD	Perimeter (mkm) χ±SD	Ratio of "circularity" (parameter ImageJ) χ±SD
Group (1a) Epithelium of fallopian tubetube without atypia	8	24.488±4.768	19.224±2.107	0.705±0.158
Group (1b) Tube intraepithelial neoplasia	6	25.881±6.664	19.623±2.607	0.691±0.095
Group (2) Serous "high-grade" OAC	12	28.912±8.090	21.257±2.558	0.681±0.145
Group (3) Metastatic peritoneal serous carcinoma: (CA125+,CK7+,CK20-,WT-1+)	6	37.987±4.972	23.504±1.766	0.767±0.104
p		p (1a, 1б)>0.05, p(1a, 2)>0.05, p(1a, 3)<0.05, p(1б, 2)>0.05, p(1б, 3)<0.05, p(2, 3)<0.05	all p>0.05	all p>0.05

Note: χ±SD – mean ± standard deviation, statistically significant difference - at p<0.05, AC – adenocarcinoma.

Analyzing morphometric findings of the studied groups in Table 2, the tendency to increase in cell nuclei "from top to bottom" from fallopian tube epithelium without atypia to metastatic serous peritoneal carcinoma similar to "high-grade" OAC is clearly observed. But a statistically significant difference was found only in the area values between peritoneal carcinoma (group 3) and all the first three subgroups (1a, 1b, 2), indicating the similarity of ovarian and tubular neoplasia with the epithelium of the uterine tube (Table 2).

The features of hormonal statuses (the number of estrogen receptors and progesterone receptors by the percentage of intranuclear reactions) of the studied groups were to demonstrate the similarity of neoplastic processes (Fig. 2). According to the diagram (Fig. 2), the number of estrogen receptors (ER) and progesterone receptors (PGR) decreased progressively from *group 1 to group 3*, with increase in cases of ER (+/-) and PGR (+/- or -) AK to 50% in *group 3*, which significantly complicated the diagnostic search for carcinomas of unknown primary site.

Analysis of IHC of expression of epidermal growth factor HER-2-new, which was also presented in Fig. 2, showed the absence of HER-2-new in *subgroups 1a and 1b. In group 2*, among OAC positive IHC reactions with the HER2 / neu marker in 2 of 12 cases (16.67%) showed a level of 2+/3+. In *group 3* among metastatic peritoneal serous carcinomas without primary known source, we obtained 2 of 6 (33%) positive HER2 2+/3+ observations, i.e. relatively twice as much as in *group 2*.

Based on the traditional model of ovarian cancer carcinogenesis, superficial ovarian mesothelioma is the most likely source of serous neoplasia, largely as a result of tubular metaplastic changes in the epithelium (Müllerian type of metaplasia) resulting from mutations due to ovulation events. But an alternative source of serous carcinoma arising from the tubular epithelium it is quite likely, which is based on a significant decreaes in the risk of salpingo-oophorectomy of the materials in women with BRCA mutations. In addition, primary fallopian tube carcinoma is very rare, compared with ovarian carcinomas [6-7].

Based on the complete removal of the ovaries and fallopian tubes in women at high risk of OAC developing, prophylactically removed salpingo-oophorectomic tissue fragments revealed small non-invasive and invasive carcinomas more often in the fallopian tubes than in ovaries [6, 10, 14].

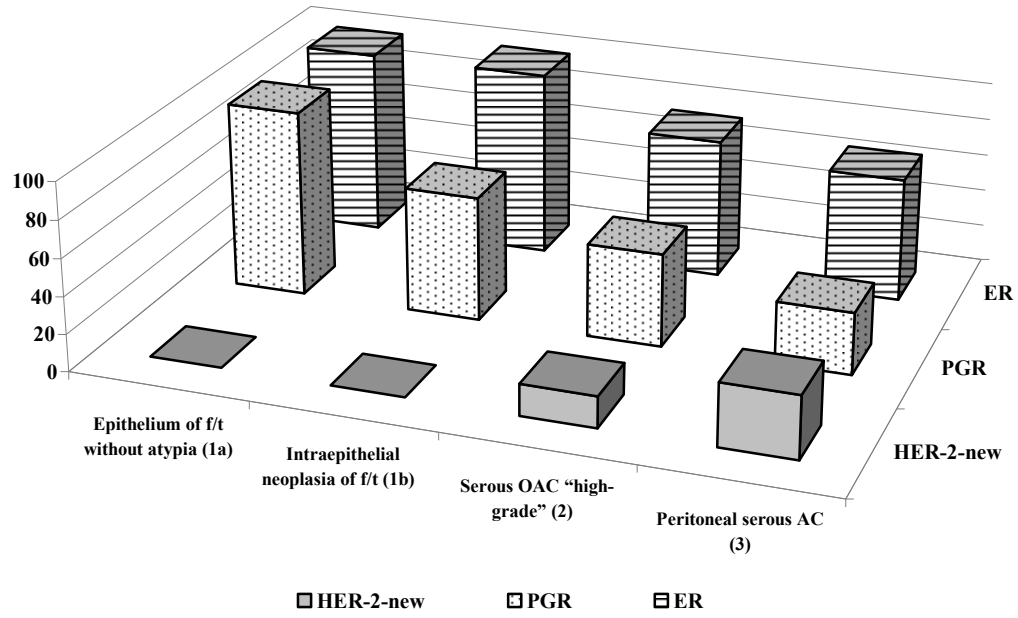

Fig. 2. Comparison of hormonal status (estrogen receptors - ER, progesterone receptors - PGR) and status by epidermal growth factor of HER-2-new tube epithelium without and with signs of intraepithelial neoplasia, serous ovarian adenocarcinoma of the variant "high-grade" and metastatic peritoneal carcinoma of serous type witho unknown primary site,%

The epithelial tumors of the removed fallopian tubes were histologically serous tubular intraepithelial carcinomas (in situ) or "high-grade" serous invasive carcinomas. Most importantly, they had a TP53 mutation identical to high-grade serous ovarian carcinoma, aberrant p53 protein expression, high proliferative activity and significant genomic instability [5, 10, 18].

Similar studies have also shown that serous tubular intraepithelial carcinomas (in situ) were found in 60% of women with "high-grade" serous invasive ovarian or peritoneal carcinomas. Fallopian tubes were obliterated by the tumor in up to 20% of cases. Finding a similarity of the TP53 mutation to Ca in situ and disseminated variants is considered as a cloning process, moreover comparing the length of telomers Ca in situ and cells associated with ovarian tumors clearly demonstrates that the former is a precursor of the latter [6, 12].

The possibility of fields of altered primary or metaplastic tube-type epithelium may also be the result of multifocal lesions, because in 15-30% of cases of "high-grade" serous invasive ovarian carcinomas or peritoneal tubes are normal without intraepithelial or invasive carcinomas, despite thorough histological study. In such cases, the ovarian superficial epithelium or epithelium of cortical inclusive cysts (CIC) may be a likely source of cancer. CICs should be lined with flat cells, similar to the superficial mesothelium of the ovaries, but most of them have cells histologically and immunohistochemically similar to the tubular epithelium that may have implanted there from the tube during ovulation [5, 15, 18].

Although "high-grade" extrauterine serous carcinomas may arise from fallopian tubes, ovaries, or rarely from the peritoneum, often the source cannot be established due to the dissemination of the disease, therein this diagnostic problem is relevant. The general characteristics of serous carcinomas of these localizations shows the same epidemiology and clinical behavior [4].

CONCLUSIONS

1. Thus, immunophenotypes of study groups (tube epithelium without and with signs of intraepithelial neoplasia, "high-grade" variant of serous ovarian adenocarcinoma and metastatic peritoneal carcinoma witho unknown primary site) revealed homogeneity in expression of CK7 (+,+/-), CK20 (-), WT-1 (+), CA125 (+, +/-) markers, with a greater affinity of carcinomas to the distal fragments of the falopian tubes (section of fimbriae).

2. The expression of p53 in all groups with signs of carcinomas (compared with control subgroup 1a without atypia) was found in two variants - negative samples (group 1b had 66.67%, group 2 – 41.67%, group 3 – 66/67%) and overexpression samples (33.33%; 58.33%; 33.33% respectively), where no

statistically significant difference was found among the mean values of p53 overexpression in study groups (p>0.05), this possibly are the links of a single pathway of carcinogenesis.

3. A morphometric study found a tendency for cell nuclei to increase from subgroup 1a to group 3. A statistically significant difference was found in the area values between group 3 and all the first three subgroups (1a, 1b, 2), indicating the similarity of ovarian and tubular neoplasia to the epithelium of the fallopian tube.

4. The number of intranuclear reactions with ER and PGR progressively decreased from group 1 to group 3, with an increase in cases of ER (+/-) / PGR (+/- or -) to 50% in group 3, significantly complicating the diagnostic search for carcinoma of unknown primary site.

5. Expression of HER-2-new revealed possible amplification (2+/ 3 + gradations) only in group 2 with OAC at the level of 16.67% and in group 3 with metastatic serous peritoneal AC at the level of 33.33%, which is relatively twice as many as in the group of primary ovarian cancers.

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