Changes in carcinoembryonic antigen and biochemical parameters in secretions from mammary glands during galactorrhea

Kebalo Dmitry¹, Zvantseva Elina², Myroshnikova Natalia³

¹ Oncologist;
Commercial rehabilitation- diagnostic center «KOMRETS»; Ukraine

² Oncogynecologist;
Zaporizhzhia Regional Antitumor Center; Ukraine

³ Laboratory doctor;
Commercial rehabilitation- diagnostic center «KOMRETS»; Ukraine

Abstract.
The purpose of the study was to study cytological, biochemical (alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), uric acid), and immunoenzymatic parameters oncomarker CA-15-3, cancer embryonic antigen (CEA), in secretions from the ducts of the milk glands to select the method and volume of surgical treatment. In 213 patients with fibrocystic disease of the mammary glands (FCD), material was taken from the discharge from the nipples of the mammary glands, using a dispenser. The material after research was divided into four groups:

1—content without proliferative changes,
2—content with proliferative changes in secretions from the ducts of the mammary glands, papillary structures were found in the secretions from the ducts of the mammary glands, single cancer cells or groups of cancer cells were found in the contents of the nipples of the mammary glands. Analysis of studies showed a gradual increase in indicators towards the fourth group compared to the first: ALT increased by - 1.40 times, (313,50 - 440,01); AST increased by - 2.15, (334,03 - 721,21); LDH increased 1.87 times (1671,64 - 3294,92); uric acid increased (2291,96 - 3813,63); SA 15-3 decreased from dec, (37965,21 - 22445,37), CEA increased by 9.34 times, (141,10 - 1318,72). A clear correlation has been established between cytological changes in the tissue of the ductal epithelium and changes in biochemical parameters in the discharge from the nipples of the mammary glands, which indicates the expediency of using this research technique for screening early forms of breast cancer, choosing tactics and the volume of surgical treatment.

Keywords: mammary gland
galactorrhea
cancer-embryonic antigen

This work is distributed under the terms of the Creative Commons Attribution-ShareAlike 4.0 International License (https://creativecommons.org/licenses/by-sa/4.0/).
Breast cancer (breast cancer) is the most common malignant disease among the female population.

According to the cancer registry of Ukraine, breast cancer ranks first in the structure of oncological morbidity among the female population. About 156,000 new cases of oncological diseases are registered in Ukraine every year, 19.6% of the female population is breast cancer. Every year in Ukraine, about 8 thousand women die from this disease, 26.5% are women of reproductive age. 21.7% of women with breast cancer seek help in a neglected state, and 11.5% of them die within a year. [13] Average life expectancy after special treatment with stage III is about 73.9% up to 5 years, and with the treatment of early forms with stage I - 92-98% live for 20 years or more. [6, 7] But, despite all the successes in cancer diagnosis mammary gland, the specific weight of detected patients with breast cancer in the early stages is insignificant. Ductal cancer occupies the first place of 71% in the morphological structure of breast cancer. [8, 14] A change in the cells of the ductal epithelium (mutation) is its response to many stimuli: hypoxia, low pH, cellular stress, cysts, the presence of one or multiple papillomas in the middle of the duct, inflammatory processes in the ducts, the influence of hereditary factors and endocrine disorders. [5, 13]

In the development of breast cancer, previous pathological processes in its tissues play a significant role, the first place is occupied by repeated dyshormonal hyperplasia with the formation of foci of fibrocystic changes (fibroadenomatosis). [16, 10] The causes of these changes in the mammary gland tissue are various endocrine disorders, often due to concomitant diseases of the ovaries, repeated abortions, improper feeding of the child, as well as previous benign tumors - fibroadenomas of the mammary gland. [9].

One of the frequent signs of changes in the ducts is discharge from the nipples (galactorrhoea). Processes in the cells of the mammary duct, more often associated with neoplastic transformation. This gives reason to think about the launch of a hidden signaling mechanism that activates many hidden functions of ductal epithelium cells and its external environment. Precursors or neoplastically
transformed cells that have appeared, secrete metabolic products, enzymes, proteins, polypeptides, different isoforms of amino acids, vascular endothelium growth factors into the ducts, which play an important role in the formation of the environment and tumor. The appearance of tumor cells leads to completely new relationships with the surrounding ENVIRONMENT. A cell of malignant cells is formed. First, how it is known that a microscopic tumor is not angiogenic and becomes angiogenic only after it reaches 1-2 mm in diameter. Due to the release of vascular endothelial growth factor (VEGF) by cells of the microenvironment and directly by tumor cells, which is an important starting factor for the formation of new blood vessels that provide nutrition to tumor cells, their ability for further growth and metastasis is preserved [17,19]. Proteins of the VEGF family have a number of biological effects, including stimulation of mitogenesis and emigration of endothelial cells, induction of proteins, remodeling of the extracellular matrix, increase in vascular permeability and maintenance of viability of newly formed vessels. [15,18]

Hyperplastic processes of the ductal epithelium or papilloma are an intermediate phase for the formation of invasive breast cancer [1,4]. Intraductal papillomas in foreign literature is a general concept that unites such conditions as solitary intraductal papillomas, multiple intraductal papillomas, ductal papillomatosis, and juvenile papillomatosis [21]. It is believed that the risk of malignancy of solitary papillomas is insignificant. At the same time, with papillomatous changes in the ducts, there is a risk of developing preinvasive ones and invasive forms of ductal carcinomas reach 23%. According to D. Debasis, the association of ductal papillomatosis with Ca in situ is almost 37% [22].

Most researchers are inclined to believe that 11-12% of patients with multiple papillomas in the ducts of the mammary gland, when they are observed for 2 years, undergo changes that lead to papilloma malignancy. [2,3] Changes in quantitative and qualitative indicators are observed, even with intermediate, locally aggressive forms of benign processes. [11,20] From 41 to 73% of breast tumors arising
in the ductal system are invasive forms of ductal cancer. [12]

All of the above provides prerequisites for the introduction of new research methods, the purpose of which is early diagnosis of the oncological process in the ducts of the mammary glands. One of these methods is the assessment of determining the presence and amount of carcino-embryonic antigen (CAR), breast cancer tumor marker CA15-3, biochemical indicators of ALT, AST, LDH, uric acid in secretions from the mammary gland.

The goal is to determine: the amount of cancer-embryonic antigen (CEA), tumor marker CA-15-3, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), uric acid in secretions from the mammary glands.

Research materials and methods
The work is based on the analysis of clinical, biochemical and immunoenzymatic results obtained in 213 patients aged from 23... to ...79 years who turned to the medical center for help with complaints of discharge from the nipples - galactorrhea. All patients underwent a cytological examination of smears-imprints of secretions from the mammary glands.

The secretions from the mammary glands were collected with a dispenser, applied to a glass slide, and dried. The liquid material was centrifuged on a CytoSpin, with a small amount of secretions, the sediment was applied to a glass slide, dried in air at a temperature of 26 degrees, the prepared smears were stained in the laboratory according to the Romanovsky method.

213 secretions from the mammary glands were studied by the enzyme immunoassay method using the analyzer (STAT FAX 303) with the use of REA test systems of the company "Vector-Best" (Russia) in a dilution of up to 300 μl.

All cytological findings Biochemical studies of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), uric acid were performed on a biochemical analyzer (STAT FAX 1901 USA). Preparations of the company BioSystem (Spain).

Enzyme immunoassays; tumor marker CA 15-3, cancer-
embryonic antigen (REA) test systems of the companies "HEMA", "VECTOR-BEST", as well as on an immunofluorescent device ("MINI VIDAS", test systems of VIDAS (France)).

Based on a visual examination of the mammary glands, patient complaints, ultrasound and mammographic examinations, patients were classified into the following groups:

1. Dyshormonal tissue changes (mastodenia) – 174 (81.69%).
2. Fibrocystic changes with pronounced proliferation of the ductal epithelium -10 (4.69%).
3. With fibrocystic changes and with intraductal papillomatosis -16 (7.51%)
4. Fibrocystic changes and suspicion of intraductal cancer - 13 (6.10%).

According to the cytological content of the research material, the patients are distributed in the following order:
3. Ingle or groups of intraductal papilloma cells - 16 (7.51%)

4. single or groups of atypical or cancerous cells - 13 (6.10%)

All patients in whom elements of intraductal papilloma or elements of intraductal cancer were detected during cytological examination were subject to surgical treatment.

Table № 1

<table>
<thead>
<tr>
<th>Cytological result</th>
<th>Histology of operative material</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>Malignant</td>
</tr>
<tr>
<td>Elements of intraductal cancer</td>
<td>1 (11,1%)</td>
<td>9 (89,9%)</td>
</tr>
<tr>
<td>Elements of intraductal papilloma</td>
<td>15 (93,34%)</td>
<td>1 (6,66%)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (61,53)</td>
<td>10 (38,46%)</td>
</tr>
</tbody>
</table>

The coincidence of the conclusions of cytologists and histologists in the group of benign changes (elements of

This work is distributed under the terms of the Creative Commons Attribution-ShareAlike 4.0 International License (https://creativecommons.org/licenses/by-sa/4.0/).
intraductal papilloma) and in the group (malignant intraductal carcinoma) was 93.34% and 89.9%, respectively.

The material was processed using the Statistica 6.1 program. The Student's t-test was used to assess intergroup differences in the values of traits with a continuous distribution, and when comparing frequency values, Pearson's $\chi^2$-test and Fisher's exact method were used.

Table № 2

| Indicator of secretions from the nipples of the mammary glands without pathological formations in the tissues of the ducts |
|---|---|---|---|---|---|
| ALT | AST | LDH | Uric acid | CA15-3 | CEA |
| n | 174 | 174 | 174 | 174 | 174 |
| average | 313,50 | 334,03 | 1671,64 | 2291,96 | 37605,61 | 141,10 |

Table № 3

| Indicator of secretions from the nipples of the mammary glands with proliferative changes in the tissues of the ducts |
|---|---|---|---|---|---|
| ALT | AST | LDH | Uric acid | CA15-3 | CEA |
| n | 10 | 10 | 10 | 10 | 10 |
| average | 354,11 | 373,10 | 1673,62 | 2665,31 | 29170,14 | 179,5 |

Table № 4

| Indicator of secretions from the nipples of the mammary glands in papillary formations in the tissues of the ducts |
|---|---|---|---|---|---|
| ALT | AST | LDH | Uric acid | CA15-3 | CEA |
| n | 16 | 16 | 16 | 16 | 16 |
| average | 394,52 | 658,75 | 1552,12 | 1786,61 | 15632,26 | 701,21 |

Table № 5

| Indicator of secretions from the nipples of the mammary glands in neoplastic formations in the tissues of the ducts |
|---|---|---|---|---|---|
| ALT | AST | LDH | Uric acid | CA15-3 | CEA |
| n | 13 | 13 | 13 | 13 | 13 |
| average | 440,01 | 721,21 | 3294,92 | 3813,63 | 22445,37 | 1318,72 |
Table № 6

<table>
<thead>
<tr>
<th>Group</th>
<th>ALT</th>
<th>AST</th>
<th>LDH</th>
<th>Uric acid</th>
<th>CA 15-3</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-я групнна</td>
<td>313,11</td>
<td>334,03</td>
<td>1757,64</td>
<td>2228,91</td>
<td>37965,61</td>
<td>141,10</td>
</tr>
<tr>
<td>2-я групнна</td>
<td>354,11</td>
<td>373,10</td>
<td>1673,62</td>
<td>2665,31</td>
<td>29170,23</td>
<td>179,50</td>
</tr>
<tr>
<td>3-я групнна</td>
<td>394,52</td>
<td>658,75</td>
<td>1852,12</td>
<td>1786,61</td>
<td>15632,26</td>
<td>701,21</td>
</tr>
<tr>
<td>4-я групнна</td>
<td>440,01</td>
<td>721,21</td>
<td>3294,92</td>
<td>3813,63</td>
<td>22445,37</td>
<td>1318,72</td>
</tr>
</tbody>
</table>

Diagram №1

ALT indicators

Diagram № 2
MEDICINE AND PHARMACY

AST indicators

Diagram №3
Indicators of LDG

Diagram №4
Indicators of Uric acid

Diagram №5
Discussion:
Diagnosis of early forms of breast cancer remains a difficult problem. In order to assess how important, the metabolic processes in the tissues of the mammary duct are when the oncological process occurs, a study was conducted. The first studies that showed an increase in biochemical processes that occur in the tissues of the mammary glands and their ducts during the formation of a cancer center during galactorrhea were made and published at the beginning of the last century. Recently, we have not come across works related to the use of CEA in the diagnosis of early forms of breast cancer.

The use of this method, which is enriched with the knowledge of previous studies, currently provides insight into the processes taking place in the cells of the ducts and their surroundings, long before the appearance of an invasive tumor lesion of the basement membrane. This is a potentially new method of research, which is the result of an active search for improving the detection results at the early stages of the formation of the oncological process in breast tissue.

Conclusions:
- The analysis of the research results shows a clear correlation between the cytological changes occurring in the ducts of the mammary glands and the changed biochemical
indicators with tumor markers. These changes in indicators to some extent confirm the stages of carcinogenesis in the tissues of the ducts of the mammary glands.

- Timely determination of changes in cytological, biochemical and immunoenzyzmic indicators (specific markers) in secretions from the ducts of the mammary glands, which confirm the changes related to the transitional state or breast cancer, enable oncologists to choose treatment tactics and the scope of surgical intervention.

- this method can be used as a screening method for diagnosing early forms of breast cancer.

- All formations that arise in the ducts of the mammary glands, regardless of their tendency to malignant transformation, are subject to removal, because sometimes they are difficult to distinguish from malignant neoplasms.

References:


Lobota I.I. Prognostic values of androgen receptor expression by breast cancer cells.//Clinical Oncology No. 1(17). 2015.


[13] Palamarchuk V.B., Plakida A.O., Datsenko G.V. Breast cancer etiological factors, clinical signs, methods of diagnosis, treatment and prevention.// Biomedical and Biosocial Anthropology


