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DIAGNOSTIC AND PROGNOSTIC VALUE OF DEFINITION OF THE ONKOFETALIC ANTIGEN OF CA-125 AT TUMORAL PROCESS IN OVARIES (REVIEW)

In the review the literary data about the modern classification of tumoral markers, diagnostic and prognostic value of definition of an onkofetalic antigen of CA-125 at tumor process in ovaries are provided. It is shown that the method of definition of the maintenance of CA-125 cannot be used for differential diagnostics non malignant and malignant tumors, however high sensitivity of a method is perspective for primary diagnostics of malignant tumors, monitoring of the postoperative period and prediction of disease.

Keywords: onkofetalic antigen CA-125, tumor, ovarian, review.

Frequency of establishment of tumours of ovaries for the last 10 years was increased from 6–11 % to 19–25 % [11]. Most tumours of ovaries are of high quality and on their part is 75–87 % all tumours of ovaries [9]. Of high quality tumours and pre-tumour new formations of ovaries occupy the second place among new formations of the reproductive system of women and are 19–25 % from all gynaecological diseases [11].

The cancer of ovaries (OC) stably occupies a fifth place among reasons of oncologic death rate of women [5] and is one of the most widespread tumours of privy parts. Peak morbidity registered after 65, thus to 10 % cases of OC inherited (domestic OC) [4]. In Ukraine a death rate from this disease remains high – 10 women from each 100 thousands population of woman [6, 28, 42, 43].

Absence of specific simptomatik, tendency to growth, possibility of malignisation of high quality tumours and pre-tumour new formations of ovaries is caused necessity of determination of factors of risk of their origin, development of

diagnostic algorithm, differentiated approach and the methods of treatment.

By researches of the last years the well-proven perspective of wide introduction in clinical practice of determination of onkomarkers with the purpose of diagnostics, estimation of prevalence of disease, choice surgical, chemotherapeutic and radial treatment which enables in time to find out relapses and remote innidiation [8, 42].

Among all known tumour markers one of the most specific and most sensible there is an antigen of CA-125 (cancer antigen), which is producted the malignant cages of ephithelial tumours of ovaries. The increase of concentration of this marker in blood of patients straight correlates with mass of tumours, stage of prevalence and process. He is the base laboratory criterion of monitoring of patients with the cancer of ovaries [3]. Dynamics of change of this level a marker at a non aduvant chemotherapy, after operative interference and at an aduvant chemotherapy in future use as a prognosis of disease, efficiency of chemotherapy and for the pre-clinyc exposure of relapse of disease [33, 38].

However possibilities of application of marker for skrining and for primary diagnostics of shrine of ovaries limited because his level can rise at some physiology states (menstruation, pregnancy), an oncologic diseases and also at presence of malignant tumours of other localisations [1]. However, without regard to it, CA-125 is the most valuable index at the estimation of efficiency of antitumors treatment and at prognostication of development of disease [15]. Especially important is determination of CA-125 for the pre-clinyc exposure of relapses.

Determination the antigen of CA-125 is widely inculcated in onkogynaecology practice. In 1981 Bastom was identified onkomarker CA-125 by mouse antibodies in the line of cages of sick woman with serosal carcinoma of ovaries [2]. Using of this test for the early exposure of disease, differential diagnostics, prognostication of flow of illness, require subsequent research and scientific ground [19, 30, 37, 40].

Modern classification of onkomarkers. Tumour markers – its matters, which appear in blood, urine or fabrics of body of patients and which are producted tumour cages or organism in reply to development of tumour. In a difference from matters

which are producted normal cages, tumour markers or have high-quality (tumour specificity) or in number (associated with a tumour, present similarly and in normal cages) [46].

There are a few classifications of oncomarkers [47].

I. On the basis of biological function:

1. Oncofetalic antigens: cancer-embryo antigen, alpha-1-phetopritein, human chorionic gonadotropin, specific beta-1-protein of pregnancy, CA-125, CA 15-3, CA 19-9, CA 50, CA 72-4 [26].

II. Enzymes: acid phosphatase of prostate, lactate dehydrogenase, neuron-specific enolase, thumidinekinase, tissue polypeptidic antigen.

III. Hormones: adrenocorticotropic hormon (ACTH), antidiuretic hormone, lactogen of placenta, calcitoninum, parathormone, prolactine.

IV. Receptors: to progesteron, to estrogen.

V. Other matters: ferritin, beta-2-microglobulin, immunoproteins.

Most tumour markers behave to the oncofetalic antigens which appear in relation to high concentrations in fabrics an embryo, on-the-spot cages, which are differentiated and play an important role in a fetation [26]. For the adults their level considerably below and a biological function is unknown [42]. Characteristically, that oncofetalic markers more frequent all present in the differentiated tumours and their level correlates with a size of tumour. Therefore determination of these markers have an important role for diagnostics, prognostication of illness and control after of treatment [46].

The level of markers of the first sub-group, as a rule, rises at the states which are characterized the expressed of cell-proliferative activity and low differentiated cages, that allows to use them for determination of prognosis and stage of disease. The second group of markers is high-specific for the differentiated tumours and that is why it is applied for determination localisation of primary tumour and also for differential diagnostics of malignant and of high quality diseases [26].

Tumour markers which have enzymic activity – it is second on prevalence group of markers, which can be divided into two sub-groups. The first is made by

enzymes, what characteristic for embryo fabrics which develop: tissue polipeptidniy antigen, timidinkinaza, neyron- specific enolaza. The second sub-group is enzymes with the set biological function in a grown human organism: lactate dehydrogenase, acidphosphatase of prostate.

Tumour markers-hormones are producted the specialized endocrine cages (for example, calcitonin is secreted of medularic carcinomas of thyroid and thyreoglobulin – by follicle its form) or synthesized ectopic (for example, similar to ACTH or horyonic gonadotropine at bronchogenic carcinoma) and more frequent all used for control after motion of medical treatment in period after operation [47].

With the increase of size hormonal active tumours the amount of receptors of hormones is increased. Unlike the previous groups of markers, which appear in the blood, in this case speech goes about tissue markers researches of which conduct in material of biopsy. These markers use for determination of prognosis and also for the choice of the most proper tactic of treatment.

To the group of oncomarkers, that does not have enzymic or hormonal activity, connections which are producted normal fabrics of organism belong, however much their concentration grows sharply, as a result of heterospecific reaction of organism on development of tumour (ferritin, 2-microglobulin, immunoproteins) [46].

In other classification tumour markers are divided into three groups:

1. Main – have a high sensitiveness and specific for concrete tumours;

2. Second-rate – less specific, than main, but at their simultaneous determination authenticity of exposure of cancer tumour rises substantially;

3. Additional – does not have high specificity to the certain type of tumours, but high organospecificly differ, that help to define possible localization of tumour process.

The markers of tumour growth also can be subdivided into different classes:

immunological are the antigens or antibodies associated with a tumour to them; hormones – (KHGCH, ACTH); enzymes as phosphotases, lactate dehydrogenase; products of exchange as a creatyne, hydroxyproline, poliamyns, free DNA; squirrel of plasma – ferritin, cerulloplazmine, β2-microglobuline, albuminous

products of disintegration of tumours.

It should be noted that the selected classes are relatively conditional, as in all classes basic is immunological principle: reaction a "antigen-antibody" which is realized *in vitro* by monoclonal antibodies.

General description of CA-125. In embryon onkofetalic antigen CA-125 meets in the ephithelial cells of respiratory and digestive highway [47]. In adults CA-125 appears in ephithelial cells. The levels of CA-125 are enhanceable set for patients with malignant diseases: ovaries, uterus, endometrian, suckling gland, pancreas, liver, line and sigma bowel, stomach, bronchial tubes.The normal content of CA-125 in the blood makes 0–30 E/ml. CA-125 is a high molecular mucin-like glycoprotein. Carbohydrate component of CA-125 presented in a greater degree a lactoglucose, n-acetyl-glukosamine, in a less degree by a n-acetil-galactosamine, glucose, manose and sial acid [36, 48, 49]. The molecule of CA-125 shows by itself one large transcript, look like the transcripts of genes of mucins [49] and consists of three basic domains. Out of cell part of albumen is presented an aminoterminal domain and large domain which is folded, approximately, no less than from 45, and possibly, more than from 60 conservative amino acid sequences which repeat oneself. An aminoterminal domain is characterized the high degree of O-glicosylation due to the presence of plenty of tailings of serine and treonin. Amino acid sequences, which make the second extra cell domain consist of 156 amino acid tailings, repeat oneself. These sequences are characterized high conservatism and identicalness of structure of ekzon. A sequence from 19 amino acid, celled between two tailings of cystein, which form a loop inwardly [49, 57], has most conservatism, and 81 from 156 amino acid tailings is conservative [57]. Supposition about the presence of conservative remain of methionine position 24 in to 156-amino acid sequences [49] experimentally were not confirmed in connection with absence of methionine [47, 57].

Use of one monoklonal antibody in first test-sistem for determination of this level an antigen in biological liquids based on existence of plural tandem repetitions in a structure extra cellular the domain of CA-125, the presence of which was confirmed a sequenation a gene [49, 57]. Existence of two antigen domains, located

close to each other was rotined [44, 48]. On the basis of it there were developed test-sistem with the use of two antibodies with different epitope specificity. It is foreseen that exactly an amino acid sequence, celled between two tailings of cystein is an imunogenic area and carries both known antigen domains [49].

Carboxyterminal of blast-furnaces consists of extra cell area which does not have a homology with other domains, typical transmembrane area and cytoplasm end. In addition, he carries a potential site for proteolytic gydrolyse. Possibly dissociating of molecules of CA-125 is explained his presence from the surface of cell [49, 57]. As specified before, phosphorylation the surface of cell is preceded dissociating of CA-125 on tailings of serine or treonyne in the cytoplasm area of molecule [29]. The presence of potential site of phosphorylating of tyrosine is described also [49, 57].

In most cases (cancer cell in a culture, standards of tissue and biological liquids) the high molecular and low-molecular forms of CA-125 are simultaneously present with molecular mass from 200 to 4000 kDa [17, 44, 48]. However the method of anion-exchange chromatography at the elution of CA-125 in the gradient of salt was found out heterogeneity of this glycoprotein after a charge [48]. It is foreseen that heterogenity of molecules of CA-125 is and after a charge and after molecular mass it is determined the different amount of tailings of sialov acids and sizes of carbohydrate chains. Albuminous part of extra cell domains has plenty of potential sites for O-glycosilation, that also can bring in certain payment in heterogenity of CA-125 [49]. In addition, both indexes change in investigation of gradual deglycosilation of lateral chains at finding an antigen in bioactive liquids [48]. The molecule of CA-125 easily degrades *in vivo*. After partial proteolysation of aminoterminal domain the different number of the repeated amino acid sequences can appear. These can explain the presence of plural molecular forms of CA-125 in different biological liquids, with different mass and charge [49]. Piling up an antigen in cell is mediated posttranslating proccesing him albuminous predecessor. The inhibitors of O-glycosylation are violated by formations of CA-125 [48]. The mechanism of this violation while is not investigational. The different variants of explanation are possible – from stopping of process of synthesis of polipeptad

chainlet in absence posttranslating O-glycosylation to rapid proteolysis anomalous synthesized an antigen.

Formation of CA-125 is observed mainly in the phase of G0/G1 of cellular cycle. On the phase of cellgrowth in a culture not found out dependence of level of expression of CA-125. Thus, the concentration of CA-125 in a culturall liquid is determined only the incurrence of cancer cells which produce an antigen and in the whey of blood of patients – by the sizes of tumour.

Method of selection of CA-125 in extra cell matrice exactly not known cells. An exposure is at cloning of gene of CA-125: to the site of the proteolytic slabbing near-by transmembrane a domain specifies on the proteolytic mechanism of freeing. Probability of synthesis of the specific secreted forms of CA-125 is however eliminated [36, 48]. In last case independent formation of diaphragm and secreted forms of this glycoprotein can be the result of alternative splaysing him mRNA [31, 57].

On this time there is unknown question about that, what forms of glycoprotein of CA-125 are secreted cells. At the study of cages of amniotic origin of line of WISH both the high molecular appeared in a cultural liquid and low-molecular (200 kDa) forms of CA-125 [48]. It was set at the use in quality probed object of cells of carcinoma of ovary of line of OVCAR-3, that in a cultural environment was secreted only high molecular form of CA-125 [36]. Considerable divergences in composition the molecular forms of CA-125 in different biological standards allow to assume existence of tissue specificity of CA-125 [17].

A synthesis and secretion of CA-125 is regulated those a way, that and proliferation of ephithelial cells. An alarm way is started the ephithelial factor of growth, which through activating of row of kinase stimulates the in cell phosphorylating of CA-125 and him next exit from cells in an environment. After one hypothesis of phosphorylating CA-125 takes place on a serine or treonine [29, 48, 49], after other – for tyrosine [57]. It is foreseen that the association of CA-125 with the surface of external membrane of cell also depends on his phosphorylating. For the secretion of this albumen from a cell or for his dissociating from a cellular surface it is needed to delete a

phosphatic group: or by limited proteolysis of phosphopeptide, or dephosphorilated of the proper amino acid remain. As a result of inhibit analysis supposition is done, that dephosphorilation of CA-125 takes place with participation of phosphotase 2B [48].

A tumour marker of CA-125 present in an organism in two forms. At treatment of microsections of different fabrics an antigen appears specific antibodies on-the-spot cells of glandular epithelium, mainly womans sexual sphere, sucklings glands, respiratory highway [36, 48, 55].

Presence a transmembrane domain confirms, that CA-125 associated with a membrane [49]. In a free form CA-125 is in different amounts in many liquid environments of organism [17, 44].

Diagnostic and prognostichna meaningfulness of determination of CA-125. Determinations of level of CA-125 in the blood found wide application in monitoring of shrine of ovaries – on the early stage at the exposure of relapses and at the estimation of efficiency of therapy [37, 40]. However in modern literature practically nothing is known about functions or physiology role of this albumen both in normal fabrics and in malignant [44, 55].

CA-125 is not especially a tumour marker, because synthesized in the normal and malignant cells of different ephithelial origin. In a norm CA-125 to expresse on the early stages of development of embryo and in two-bits it appears in amnioni, chord, channel and alantoise, derivatives of colomn epithelium [47]. For adults this antigen appears on-the-spot ephithelial cells of fallopies tube, endometrium, neck of uterus, sweat-glands, sucklings glands, bronchial tubes. His being in a seminal liquid, pectoral milk, vaginal excretions, amniotic liquid, caliva, pleura allows to assume that CA-125 is the normal secretory product of row of the proper epitheliums [17]. In a small concentration CA-125 present in the whey of blood of healthy people. Concentration of it an antigen in the secret of mucus epithelium considerably exceeds his concentration in the whey of blood of healthy human [17, 55].

At diseases the level of CA-125 in the whey of blood grows in the first turn at the various gynaecological (cancer of endometrium, carcinomas of ovaries and fallopies tube) and ungynaecological (carcinoma of sucklings glands, lights) forms of shrine [18,

32, 35]. In the two-bit of cells the level of CA-125 in the whey of blood grew at carcinoma of gastroenteric highway, pancreas, thick and direct bowel [18, 35]. The increase of concentration of CA-125 in the whey of blood can take place and at of high quality gynaecological diseases – ovaries [34], endometriosis, fibromioma of uteruses, and also at the inflammatory diseases of organs of abdominal region and lights [24, 34, 50]. Increase of level of CA-125 in the whey of blood for patients with of high quality and especially malignant tumours, and also at other diseases, probably, it is determined growth of amount of cells which are quickly divided [41].

Determination of level the antigen of CA-125 in the whey of blood finds application in monitoring of shrine of ovaries [3, 33, 38]. Changes of this index are in relation to a maximum value at raising of diagnosis, in the process of treatment and next clinical supervision most adequately reflect a dynamics exactly of this disease [30, 37, 40]. The enhanceable level of CA-125 for patients with different carcinomas of ovaries was observed in 40–95 % cases depending on a diagnosis, stage of disease and histological type of tumour. From other data the change of level of CA-125 correlated with clinical motion a disease in 87–94 % cases [25]. At the of high quality tumours of ovaries of increase of level of CA-125 it took place only in 8 % cases [19, 41, 58]. This tumour marker was offered for diagnostics of shrine of lights, but it appeared that the increase of level of CA-125 in the whey of blood of such patients had taken place not more than in 40 % cases [41].Through the considerable vagueness of molecular properties of CA-125 a standard is for this glycoprotein while vidsutniy [20, 34], that is why quantitative estimation of level an antigen conduct in conditional units of O/ml. For healthy women the source of CA-125 in endometrium and as a diskriminaciyniy level of CA-125 is used index 35 O/ml [12]. A concentration of CA-125 is in the whey of blood in 95–99 % healthy women are not exceeded by this level [35]. Mean values of concentration of CA-125 for healthy women, got in different laboratories, considerably differentiate between itself, though does not exceed the accepted boundary value. It becomes firmly established that the middle levels of CA-125 differentiate for women which belong to the different ethnic groups, however much information, got the independent groups of researchers, conflict with each other [34, 51].

The level of CA-125 in the whey of blood of women considerably changes during a menstrual cycle [3, 33, 38]. CA-125 grows during menstruation, and then falls. Some researchers discovered that the level of CA-125 is identically low in a follicule and lyutein phases [21]. After a supervision other, the gradual decline of concentration of CA-125 to the level of boundary value takes place only in the lyutein phase of cycle [45]. During pregnancy the level of CA-125 grows insignificantly [34].

The concentration of CA-125 in the whey of blood changes with age. For healthy women the individual changes of mean values of this index are insignificant to 40 years, and with the offensive of postmenopause place is taken him substantial decline. In a number of cases there can be some increase of level of CA-125 during absence of pathology for women more senior 60 years [34]. Smoking and use of coffee practically does not influence on content of CA-125 in the whey of blood [34, 51].

Presence of the expressly expressed vibrations in the level of CA-125 for healthy women during a menstrual cycle, at age-old changes and in many other cases (anovulatory cycle, pregnancy, gisterektomiya, endocrinotherapy, peroral contraception) is a persuasive argument for stopping of the use of boundary value 35 O/ml in quality general for all women [34, 51]. It is suggested to set different boundary values for women which are in genesial and climacteric periods [22, 45], and for women in genesial age – a few boundary values which take into account the stage of menstrual cycle [45].

Most successfully a test on the level of CA-125 in the whey of blood of patients with carcinomas of ovaries is used for the estimation of efficiency by a chemotherapy after operative interference and at the clinical supervision of patients with the purpose of early exposure of relapses [3, 14, 33, 38]. It is set that the level of CA-125 rose 3–6 months prior to the display of clinical symptoms of relapse of disease. However found out it is to next time, that is the desckriminacing level (DL) of content of CA-125 for the operated patients [12].

Using of this test for the early exposure of disease, differential diagnostics, prognostication of flow of illness, require a subsequent ground [19, 30, 37, 40]. The method of single determination of level of CA-125 in the whey of blood of patients has

neither a sufficient sensitiveness (percent of correct positive diagnoses) nor specificity (percent of correct negative diagnoses), to be used in clinical and differential diagnostics. The single measurings do not allow to set divergence between the early (I and II) stages of shrine of ovaries and by of high quality tumours. It is explained the considerable ceiling of levels of CA-125 in the area of low values for healthy women and for patients with new formations of ovaries [34]. At monitoring of shrine of ovaries the leadthrough of serial determinations of CA-125 is recommended. Especially it touches women in which was found out enhanceable maintenance an antigen to surgical interference [56]. Now set practice of testing each 3–4 months during two first years after the leadthrough of treatment [19, 30].

An exposure of shrine of ovaries on the early stages is major pre-condition of increase of duration of survival of patients after treatment. However much the use of tests on CA-125 in skrining of crawfish of ovaries remains the most contradictory questions through low positive prognostic possibilities of method [28, 42, 43].

A sensitiveness of test for determination I stage of carcinomas of ovaries is not more than 50 %. It means that in the half of cases present tumours do not appear this method by a size less than 1 sm [30, 40]. Periodic analyses on the level of CA-125 in the whey of blood of such patients of must be accompanied intravaginal by ultrasonic research [30, 55].

In the first years application of test was discussed question about establishment of two maximum values of CA-125 – 35 and 65 O/ml. Content of CA-125 below 35 O/ml in the whey of blood of women approximately meant absence of some diseases of ovaries. Increase of level an antigen to 65 O/ml foresees the presence of of high quality disease and exceeding of this value – specifies in the presence of malignant process. The analysis of level of CA-125 to operative interference with the results of histological researches rotined that only in 2 % with the of high quality diseases of ovaries the boundary value of this tumour marker exceeded patients 65 O/ml. It is presently recommended to conduct testing of CA-125 each 3–4 months during two first years after the leadthrough of treatment, then analyses can be done rarer, but regularly. At the same time in the first two weeks after an operation the level of CA-125 can be enhanceable by

comparison to a pre-operation period from the considerable damage of fabrics, that is why to begin determination of CA-125 expediently through a month after operative interference [16, 23]. After operation speed of decline of level of CA-125 represents both the measure of radicalism of operation and efficiency of non-aduvant chemotherapy which is conducted. Speed of decline of level of CA-125 in the whey of blood of patients allows adequately to estimate efficiency of select post-operative therapy [25]. An enhanceable level of CA-125 after an operation is the index of presence of remaining tumour, while a normal level can be observed both in default of and at presence of tumour [13]. The gradual increase of content of CA-125 in the whey of blood of patients after surgical interference testifies to progression of tumour [16]. Makes test-sensitivity early exposure of relapse carcinomas of ovaries this method 80 % [52, 54].

In 27 % patients malignant tumours were classified as of high quality. To the sensitication method and his application for early and differential diagnostics simultaneous determination of a few tumour markers can promote in addition to CA-125 [37].

The level of CA-125 to beginning of course of chemotherapy not informing in relation to survivability of patients [26]. Speed of decline of level of CA-125 on the early stages of chemotherapy is an important factor for the prognosis of survival of patients with carcinomas of ovaries. Depending on the interval of time (less than 20 days, from 20 to 40 or more than 40 days) survivability more than 2 years after primary treatment is 76, 48 or 0 % accordingly [26, 37]. This index allows to do a short-term prognosis only [40]. For more long-term prognosis determination of absolute level of CA-125 and his content is recommended after application of three courses of chemotherapy [55]. The individual values of other kinetic index of CA-125 – to time of doubling of his level – vary scope from 5 to 375 days. The absolute values of content remove probability of relapse of shrine of ovaries [53].

Mionectic in comparing to the boundary value 35 O/ml the indexes of level of CA-125 can find application in the exposure of gynaecological diseases of other character. In opinion of some researchers, diminishing of concentration of CA-125 in the whey of blood of pregnant to 10 O/ml and below, that is accompanied the uterine

bleeding in the second half of pregnancy, specifies on high probability of premature births [39]. Indeed, for women with ordinary stoped of pregnancy concentration of CA-125 below than in a control group [27].

The analysis of data of world literature testifies that the method of determination of content of CA-125 can not be used for differential diagnostics of of high quality and malignant new formations. However much high test-sensitivity (from 75 to 90 %) is perspective for diagnostics of relapse of malignant new formations, monitoring of after operation period, and prognostication of flow of illness.

Conclusions

1. Increase of content the antigen of CA-125 to 65 O/ml testifies to the presence of high quality new formation, and exceeding of this value – specifies in the presence of malignant new formation.
2. A sensitiveness of determination of content of CA-125 for diagnosticating I stage of carcinomas of ovaries is not more than 50 %, and for the early exposure of replase carcinomas of ovaries is 80 %.
3. After operation speed of decline of level of CA-125 represents both the measure of radicalism of operation and efficiency of non-aduvant chemotherapy.
4. In a post operative period an enhanceable level of CA-125 in the whey of blood is the index of presence of remaining tumour, and the gradual increase of content of CA-125 testifies to progression of tumour.
5. Speed of decline of level of CA-125 on the early stages of chemotherapy is an important factor for the prognosis of survival of patients with carcinomas of ovaries.

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