THE SIGNIFICANCE OF DETERMINING HORMONES AND TUMOR MARKERS IN BLOOD SERUM IN GRANULOSA CELL TUMOR, ITS RECURRENCES AND METASTASES

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Abstract: *according to Kerzhkovskaya N.S. and her colleagues, the final diagnosis of granulosa cell tumor is made only on the basis of histological examination. In addition to the standard scope of diagnostic measures, which includesgeneral blood and urine tests, tests for markers CA-125, HE4, ROMA, CA-199, ultrasound of the abdominal organs, lung radiography, mammography, gastro- and irrigoscopy, aspiration biopsy of the endometrium, patients with If GCT is suspected, a blood test for sex steroids and inhibin, which are highly specific for this pathology, is indicated. According to indications, hysteroscopy and separate diagnostic curettage, computed tomography, laparoscopy, radioisotope study of renal function and excretory urography are performed.[5]*

Keywords: *granulosa cell tumors of the ovaries, granulosa cell tumors of the adult type ovaries, juvenile granulosa cell tumors, follicle-stimulating hormone, luteinizing hormone, inhibin A and B, estradiol, menstrual cycle*

Аннотация: *по Кержковской Н.С. и ее коллег окончательный диагноз гранулезоклеточной опухоли ставится только на основании гистологического исследования. Помимо стандартного объема диагностических мероприятий, включающего общие анализы крови и мочи, анализы на маркеры CA-125, HE4, РОМА, CA-199, УЗИ органов брюшной полости, рентгенографию легких, маммографию, гастро- и ирригоскопию, аспирационную биопсию. эндометрия, пациенткам с ГКТ. При подозрении на ГКТ показано исследование крови на*

половые стероиды и ингибин, высокоспецифичные для данной патологии. По показаниям проводят гистероскопию и раздельное диагностическое выскабливание, компьютерную томографию, лапароскопию, радиоизотопное исследование функции почек и экскреторную урографию.[5]

Ключевые слова: *гранулезоклеточные опухоли яичников, гранулезоклеточные опухоли яичников взрослого типа, ювенильные гранулезоклеточные опухоли, фолликулостимулирующий гормон, лютеинизирующий гормон, ингибин А и В, эстрадиол, менструальный цикл.*

Burger H.G. in his work assigns a significant role in the diagnosis of GCT to tumor markers. Ovarian GCTs produce a range of steroid and glycoprotein hormones. Each of the substances secreted by the tumor can be used as a serum marker for the diagnosis of neoplasms and monitoring of women suffering from this pathology. Inhibins are a diverse family of glycoprotein hormones synthesized only by the ovaries and placenta, suppressing the secretion of FSH by the pituitary gland. Of particular interest from this perspective is immunoreactive inhibin, which includes inhibin dimers (inhibin A (α A) and inhibin B (α B)) as well as free α subunits. Several researchers working on the treatment and monitoring of inhibin levels in patients with granulosa cell tumors have come to the following conclusions. In the plasma of menopausal or castrated women, inhibin levels are extremely low (<5 pg/ml), which determines the high specificity of inhibin as a tumor marker. In women of reproductive age, their blood concentrations fluctuate depending on the phase of the menstrual cycle, peaking in the ovulatory and early luteal phases.

Many specialists believe that the tumor-associated marker CA-125, used in monitoring serous ovarian cancer, is not a specific marker for GCT, however, its use can be useful in differential diagnosis.

Livshits writes in his article that in the case of hormonally inactive granulosa cell tumors and, consequently, in the absence of signs of hormone production, GCT can be extremely aggressive and poorly responsive to treatment.

The material for studying the examination methods included outpatient cards, ultrasound studies, mammography data, medical histories, results of histological and cytological studies, blood tests for the tumor marker CA-125 and inhibin A and B. In total, data from the examination of 34 patients with ovarian granulosa cell tumors from 2001 to 2021 were analyzed, who passed through the gynecological department of the Andijan branch of the Republican Specialized Scientific and Practical Center for Oncology and Radiology. Of these, 5 were juvenile GCTs and 29 were adult GCTs.

Research results: The study on the content of serum hormones and tumor markers in women with GCT and practically healthy castrated women consists of 46 observations. In all women with granulosa cell tumors, the primary tumors were removed in the first stage of treatment. Thirty-four women were actively summoned for reexamination and blood sampling to determine serum hormones and tumor markers. The first group included 3 young women previously operated on for GCT, involving unilateral adnexectomy, biopsy of the contralateral ovary, and resection of the large bowel. The second group consists of 14 women operated on for Regarding GCTs in the scope of extirpation and vaginal amputation of the uterus with appendages, including resection of the greater omentum. The third group consists of 17 women who, upon reexamination, were found to have disease recurrence, metastases, or residual manifestations. For the control group, 12 women who underwent panhysterectomy more than a year ago due to cervical cancer, but without hormone-producing tumors in the history and without signs of the disease at the moment, were selected.

The researched groups		Inhibin A (pg/mL)	Inhibin B (pg/mL)	FSH (IU/L)	CA 125 (IU/mL)	Estradiol (pmol/L)
Patients without signs of progression	with one ovary (n=3)	34,5 (15-76)	43,6 (4,4-90.1)	8,2 (1,1-30.3)	25,0 (5,7-74)	211 (85-255)
	Without	2,0 (0,8-	2,2 (0.4-	57,4 (21.8-	15,8 (7.4-	23 (6.3-42.4)

	ovaries (n=14)	7.2)	6.3)	110)	60)	
Patients with recurrences and metastases (n=17)		17 (0,6-80.0)	300 (203-556)	31,1(7,0-90.3)	35,4 (6,5-183)	281,4(180- 445)
Control group (n=17)		3,1 (0,5-6.0)	2,4 (0-3.5)	66,4 (43.1-105)	16,5 (4.2-31)	28(10,1-38)

Table 1

This table shows that the comparative analysis of inhibin A, inhibin B, FSH, CA-125, and estradiol in women after hemi-castration, as well as in patients with GCT recurrences and metastases, significantly differs from those indicators in practically healthy women after castration, i.e., the control group, and women without ovaries without signs of GCT at present. In the first group, women were younger than those in the other groups, and they had preserved menstrual function. In light of these circumstances, evaluating such indicators as inhibin, FSH, and estradiol poses difficulties, as these indicators change depending on the phase of the menstrual cycle, but due to certain circumstances, we could not adhere to these rules in our work. The average level of inhibin A was 34.5 pg/mL, significantly higher than in the other participants, especially in castrated practically healthy women. However, in women with recurrences and metastases, the average level of inhibin A was 17, which was lower than in women with unilateral adnexectomy but higher than in practically healthy castrated women. Considering that this hormone is produced in ovarian tissues and tumors, our data confirm the possibility of using it to monitor women after undergoing bilateral adnexectomy. When determining FSH, it is worth noting that the higher the inhibin, the lower the FSH, indicating a reverse relationship between them. A similar trend was observed between FSH and estradiol, where lower estradiol levels corresponded to higher FSH levels. Thus, in women with unilateral adnexectomy, the average FSH level was 8.2 mIU/mL. In women with castration without signs of disease, their levels were significantly higher - in the second group,

the average level was 57.4 mIU/mL, and in the control group, it was 66.4 mIU/mL. Interesting results were observed in women with recurrences and metastases, with an average FSH level of 31.1 mIU/mL. This can be attributed to the fact that this hormone is produced by the hypothalamus, and its level depends on the blood levels of inhibins and estradiol; the lower the latter, the higher the FSH level. The determination of the average CA-125 level did not provide sufficient information. Yes, there were some differences in its content among women in different groups, but there were cases of a sharp increase in CA-125 levels in some women to 80. However, upon re-evaluation a couple of months later, these levels normalized and were not related to recurrences and metastases. Thus, in the first group, the average CA-125 level was 25 U/mL, within the normal range. In the second group, the average level was 15.8. In the third group, i.e., in the group with disease manifestations, it was slightly above the norm at 35.4. However, as mentioned earlier, this could have been a coincidence. In the control group, the average level was 16.5 U/mL. Estradiol in women after hemi-castration was within the normal range, at 211 pmol/L. However, considering that the timing of the tests was not adhered to according to the menstrual cycle phase and the small number of observations, these data can be considered relative. Women with recurrences and metastases showed significantly higher levels (281.4 pmol/L) compared to practically healthy women after castration. In addition to the ovaries and tumors, estradiol is produced in the adrenal glands and adipose tissue, which is why low concentrations were detected in castrated women. Thus, in the second group, the average level was 23 pmol/L, and in the control group, it was 28 pmol/L. It can be said that inhibin B had the greatest sensitivity to recurrences and metastases. In women after hemicastration, the average level was 43.5 pg/mL. In women with recurrences and metastases, the average concentration of inhibin B was 300 pg/mL, significantly higher than in the first group and the other practically healthy women after castration. In the second group, the average levels were 2.2 pg/mL, and in the control group, it was 2.4 pg/mL. The results are visually presented in Diagram 9. An interesting observation was made in

one observed case of a recurrence Diseases where levels of inhibins and estradiol were practically zero, with subsequent indicators. The patient died within 2 months; the recurrence of the disease was very aggressive. We reviewed several studies that pointed to the connection between low hormone production levels and tumors, indicating a high level of tumor cell anaplasia and a severe course of the disease. Perhaps our observation was confirmation of this.

In conclusion, it can be concluded that when monitoring patients with granulosa cell ovarian tumors for the presence of recurrences and metastases, as well as for assessing the effectiveness of treatment, a comprehensive examination of inhibin A, inhibin B, FSH, and estradiol levels is necessary. They will help predict the course of this type of neoplasm.

Conclusions. Inhibin A, inhibin B, and estradiol are adequate serum oncomarkers for monitoring women with granulosa cell ovarian tumors in the postmenopausal period and after complete castration.

1. CA-125 is not valuable for monitoring this disease.

2. However, inhibin A, inhibin B, FSH, and estradiol are unsuitable for monitoring women with granulosa cell ovarian tumors in the reproductive age who have undergone hemicastration.

3. The absence of hormone synthesis by tumor cells is associated with high atypia, advanced stages, low differentiation, and a poor course of the disease.

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