

Ultrasonographic features and CA125 levels of hormonally active ovarian tumors

Cechy ultrasonograficzne oraz poziom CA125 w hormonalnie czynnych guzach jajnika

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Abstract

Objectives: Subjective ultrasonographic assessment is currently considered to be the best method of differentiation between various types of ovarian tumors. The aim of the study was to evaluate selected ultrasonographic features and CA125 levels of hormonally active ovarian tumors.

Material and methods: A total of 1135 women with ovarian tumors were diagnosed between 2006 and 2014 at the Division of Gynecologic Surgery, Poznan University of Medical Sciences. Within these tumors, there were 60 hormone-secreting ovarian tumors, including: 20 granulosa cell tumors, 28 fibrothecomas, 10 dysgerminomas, 2 struma ovarii, and 9 metastatic ovarian tumors. The tumors were evaluated by ultrasonography according to the International Ovarian Tumor Analysis group criteria. Additionally, we evaluated serum CA125 levels in all patients.

Results: Granulosa cell tumors occurred most frequently as large unilocular-solid cysts, moderately to highly vascularized, with low-resistance vascularization. Dysgerminomas were predominantly large unilocular-solid cysts or purely solid tumors, with minimal to moderate low-resistance vascularization. Fibrothecomas were solid masses with minimal, high-resistance vascularization. Struma ovarii occurred as small, solid masses with abundant, high-resistance vascularization. Metastatic ovarian tumors presented mainly as multilocular-solid tumors with strong, low-resistance vascularization. Papillary projections were most frequently observed in metastatic tumors and granulosa cell tumors in 56% and 50% of the cases respectively, although only half of granulosa cell tumors papillary projections exceeded 3mm. Elevated CA125 levels were found only in metastatic ovarian tumors.

Conclusions: Hormonally active ovarian tumors present several ultrasonographic features which may facilitate preoperative diagnosis.

Key words: **ovarian neoplasm / ultrasonography / CA125 / ovarian cancer /**

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Streszczenie

Cel pracy: Subiektywna ocena ultrasonograficzna jest obecnie uważana za najlepszą metodę różnicowania poszczególnych typów guzów jajników. Celem pracy była ocena wybranych cech ultrasonograficznych guzów oraz poziomu CA125 w surowicy u pacjentek z hormonalnie czynnymi guzami jajnika.

Materiał i metody: Analizie poddano 1135 kobiet z rozpoznanymi guzami jajnika w latach 2006 do 2014, leczonych w Klinice Ginekologii Operacyjnej Uniwersytetu Medycznego w Poznaniu. Rozpoznano 60 hormonalnie czynnych guzów jajnika w tym: 20 ziarniszczyków, 28 włókniakootoczek, 10 rozrodczaków i 2 wola jajnikowe. Do badania włączono również 9 guzów przerzutowych jajnika. Guzy były oceniane w badaniu ultrasonograficznym wg kryteriów grupy International Ovarian Tumor Analysis i w surowicy pacjentek zmierzono stężenie CA125.

Wyniki: Ziarniszczyki występowały zazwyczaj jako jednokomorowe torbiele z elementem litym o umiarkowanym lub silnym niskooporowym unaczynieniu, włókniakootoczkowiaki najczęściej były dużymi guzami litymi, o minimalnym unaczynieniu o charakterze wyskooporowym. Rozrodczaki występowały z podobną częstością jako jednokomorowe torbiele lub lite guzy, z umiarkowanym lub silnym unaczynieniem o charakterze niskooporowym. Guzy przerzutowe przyjmowały najczęściej formę guza wielokomorowego z elementem litym. Wyrośla endofityczne były najczęściej obserwowane w guzach przerzutowych oraz ziarniszczykach, odpowiednio w 56% i 50% przypadków, aczkolwiek tylko połowa wyrośli endofitycznych ziarniszczyków była większa niż 3 mm. Podwyższony poziom CA125 występował tylko w przypadku guzów przerzutowych jajnika.

Wnioski: Guzy jajnika hormonalnie czynne posiadają kilka cech ultrasonograficznych, które mogą ułatwiać diagnozę przedoperacyjną.

Słowa kluczowe: guz jajnika / ultrasonografia / CA125 / rak jajnika /

Introduction

Hormonally active ovarian tumors are relatively rare, constituting about 6% of all ovarian tumors [1]. They are diagnosed both, in premenopausal and postmenopausal women. The majority of hormone-secreting ovarian tumors belong to two histological groups: sex cord-stromal tumors and germ cell tumors [2, 3]. However, almost every type of ovarian tumor, including tumors of the epithelial origin, may have functional stroma secreting estrogens, androgens and, rarely, progestagens. Mucinous and endometrioid cystadenomas and metastatic ovarian tumors are especially associated with functional stroma [4-10].

Differential diagnosis of ovarian tumors remains a challenge for gynecologic oncologists [11, 12]. Transvaginal ultrasonography is currently used worldwide, and subjective ultrasonographic assessment is considered to be the best method of differentiation between malignant and benign tumors [13, 14]. This method of evaluation requires broad experience and knowledge about ultrasonographic features of ovarian tumors. Unfortunately, the number of reports concerning ultrasonographic appearance of hormonally active ovarian tumors is limited. Although mucinous and endometrioid cystadenomas have a well-documented ultrasonographic morphology, ultrasonographic characteristics of other types of hormone-secreting ovarian tumors have been less thoroughly reported [15]. Thus, the main aim of the study was to evaluate selected ultrasonographic features and CA125 levels of hormone-secreting ovarian tumors belonging to the group of sex cord-stromal tumors, germ cell stromal tumors, and metastatic ovarian tumors.

Material and methods

The study included 1135 patients (836 pre- and 299 postmenopausal) who were diagnosed and treated due to ovarian tumor at the Division of Gynecologic Surgery, Poznan University of Medical Sciences, Poznan, Poland between 2006

Table 1. Histopathological types of analyzed tumors.

Histopathological diagnoses	amount
Simple cyst	133
Endometrioma	203
Corpus luteum cyst	59
Mature teratoma	115
Serous cystadenoma	65
Mucinous cystadenoma	64
Hemorrhagic cyst	13
Hydro-salpinx	14
Tubo-ovarian abscess	19
Fibroma	13
Thecoma	15
Brenner tumor	4
Myoma	9
Serous adenocarcinoma	151
Mucinous adenocarcinoma	29
Endometrioid adenocarcinoma	44
Clear – cell adenocarcinoma	19
Undifferentiated carcinoma	68
Dysgerminoma	10
Other germ cell tumors	5
Granulosa cell tumor	20
Borderline tumor	54
Metastatic tumors	9

and 2014. Every tumor was evaluated by ultrasound according to the following criteria: 1) tumor structure according to the International Ovarian Tumor Analysis (IOTA) criteria (unilocular cyst, unilocular-solid cyst, multilocular cyst, multilocular-solid cyst, solid tumor, not classifiable), 2) tumor volume (in cm³), 3) vascular features (Color Doppler - IOTA group scale, and spectral Doppler indexes: RI, PI, PSV), 4) and internal wall structure (smooth, papillary projection <3 mm, papillary projection >3mm, solid tumors, other) [16]. Out of all analyzed tumors, we selected tumors known for their hormonal activity and the study group consisted of 60 hormone-secreting ovarian tumors, including 20 granulosa cell tumors, 28 fibrothecomas, 10 dysgerminomas, and 2 struma ovarii. There were also 9 metastatic ovarian tumors.

Serum CA125 level was measured within 5 days before surgery. Local Ethics Committee approved of the study. All statistical analyses were conducted with the software "R" version 3.1.2 (2014-10-31), with "XNomial" library, version 1.0.1.

Results

Median and range of patient age presented as follows: granulosa cell tumors 46 (33 – 72); fibrothecomas 54 (18 – 70); dysgerminomas 19 (12 – 25); and metastatic ovarian tumors 44 (33 – 72) years of age. There were two patients with struma ovarii (30 and 47 years of age).

Granulosa cell tumors occurred most frequently as unilocular-solid cysts ($p=0.006$). Fibrothecomas were purely solid tumors in the majority of the cases ($p<0.001$). Dysgerminomas occurred as unilocular cysts and as solid tumors with the same frequency ($p=0.015$). Although most metastatic tumors occurred as multilocular-solid tumors, the evidence for it be the most frequent case is insufficient ($p=0.067$). Multinomial Goodness-Of-Fit Test was used to verify the statistical hypotheses in all cases. Struma ovarii were exclusively found as solid tumors. Ultrasonographic appearance of ovarian tumors according to the IOTA criteria is summarized in Table II.

Table II. Tumor structure according to the IOTA criteria.

	Granulosa cell tumor	Fibrothecoma	Dysgerminoma	Metastatic tumors	Struma ovarii
	% (n)	% (n)	% (n)	% (n)	% (n)
unilocular cyst	5.0% (1)	3.6% (1)	0% (0)	0% (0)	0% (0)
unilocular-solid cyst	40.0% (8)	3.6% (1)	40.0% (4)	11.1% (1)	0% (0)
multilocular cyst	5.0% (1)	10.7% (3)	0% (0)	11.1% (1)	0% (0)
multilocular-solid cyst	30.0% (6)	10.7% (3)	20.0% (2)	55.6% (5)	0% (0)
solid tumor	20.0% (4)	67.9% (19)	40.0% (4)	22.2% (2)	100% (2)
not classifiable	0% (0)	3.6% (1)	0% (0)	0% (0)	0% (0)

Table III. Diameter and volume according to the histological type of the tumor.

Histopathological diagnosis	Median tumor diameter – cm (range – cm)	Median tumor volume – cm ³ (range – cm ³)
Fibrothecoma	7.9 (3 – 25)	215.4 (13.2 – 5847.8)
Granulosa cell tumor	10 (4.2 – 25)	414.5 (32.6 – 6497.6)
Dysgerminoma	15.4 (7.2 – 22.8)	286.1 (110.0 – 3735.1)
Metastatic Ovarian Tumors	13 (7.6 – 18.5)	871.9
Struma ovarii	2.5 and 3.2	6.5 and 8.9

Table IV. Color and spectral Doppler characteristics of the analyzed tumors.

	Color Doppler Score median (range)	Pulsatility Index (PI) median (range)	Resistance Index (RI) median (range)	Peak Systolic Velocity (PSV) median (range)
Fibrothecoma	2 (1-3)	1.31 (1.00 – 3.8)	0.64 (0.5 – 0.9)	23.8 (9.2 – 35.4)
Granulosa cell tumor	3 (1-4)	0.81 (0.44 – 1.4)	0.45 (0.38 – 0.72)	31.6 (9.8 – 45.3)
Dysgerminoma	3 (2-3)	0.88 (38 – 1.1)	0.45 (0.38 – 0.69)	30.2 (8.3 – 44.6)
Metastatic Ovarian Tumor	3 (1-4)	0.72 (0.45 – 0.96)	0.38 (0.29 – 0.61)	37.6 (11.8 – 49.6)
Struma ovarii	4	1.11 and 1.02	0.65 and 0.62	38.5 and 34.2

Table V. Internal wall structure of the analyzed tumors.

	Granulosa cell tumor	Fibrothecoma	Dysgerminoma	Metastatic Ovarian Tumor	Struma ovarii
	% (n)	% (n)	% (n)	% (n)	% (n)
smooth	30.0% (6)	10.7% (3)	40.0% (4)	22.2% (2)	0% (0)
papillary projection <3 mm	25.0% (5)	10.7% (3)	0% (0)	0% (0)	0% (0)
papillary projection >3mm	25.0% (5)	7.1% (2)	20.0% (2)	55.6% (5)	0% (0)
solid tumors	20.0% (4)	67.9% (19)	40.0% (4)	22.2% (2)	100% (2)
other	0% (0)	3.6% (1)	0% (0)	0% (0)	0% (0)

Table VI. Median and range of the CA125 levels.

Granulosa cell tumor	Fibrothecoma	Dysgerminoma	Metastatic Ovarian Tumor	Struma ovarii
30.9 (7.4–172.4)	24.6 (7.1–228.1)	30.52 (21.3–39.8)	116.1 (38.4–816.2)	not available

All tumors were similar in size, but struma ovarii tended to be smaller than all other types. Table III presents median diameter and median volume of the analyzed sub-group of tumors. Most tumors were moderately to highly vascularized ($p < 0.001$; Wilcoxon signed rank test with continuity correction). However, fibrothecomas as well as dysgerminomas never scored 4 in the Color Doppler scale, whereas struma ovarii scored 4 in both cases. Spectral Doppler examination revealed that fibrothecomas are characterized by high-resistance flow ($p = 0.005$), while granulosa cell tumors, metastatic ovarian tumors, and dysgerminomas present low-resistance flow ($p < 0.001$, $p = 0.013$, $p = 0.005$). One sample t-test was used in all four abovementioned cases, with the assumption that low-resistance flow is indicated by $PI < 1.0$. The results of color and spectral Doppler analyses are summarized in Table IV.

Papillary projections were observed in 50% of granulosa cell tumors, indicating their prominent ultrasonographic feature ($p = 0.005$). However, only 25% of granulosa cell tumors had papillary projections of > 3 mm. Although papillary projections appeared in 56% of metastatic tumors, the evidence is not sufficient to claim it as the most frequent structure of the internal wall ($p = 0.15$). The structure of the internal wall is shown in Table V. A Multinomial Goodness-Of-Fit Test For was used to verify the frequency of papillary projections.

Median CA125 levels in granulosa cell tumors, fibrothecomas, and dysgerminomas were within the normal range ($p = 0.37$, $p = 0.13$, and $p = 0.14$, respectively). Elevated CA125 levels were found only in metastatic ovarian tumors ($p < 0.001$). CA125 levels were not analyzed in patients with struma ovarii. Table 6 presents the results of CA125 evaluation of the ovarian tumors. We compared medians of CA125 levels with normal CA125 distribution.

Discussion

Our paper described the sonographic patterns and CA125 concentration of hormonally active ovarian tumors. In our study, granulosa cell tumors appeared in most cases as large, cystic masses with solid component (unilocular-solid or multilocular-solid cyst), which tends to be moderately to highly vascularized. This observation is similar to the findings of Van Holsbeke et al., who reported granulosa cell tumors to be large multilocular-solid masses with a large number of locules or solid tumors with increased vascularity [17]. Kim et al., reported a series of 16 granulosa cell tumors, including 62.5% of cystic tumors with solid component and 37.5% purely solid tumors [18]. Ko et al., found that 61% were multilocular-solid and 31% were solid [19]. However, Alcazar et al., reported that 75% of granulosa cell tumors were purely solid [1]. We observed papillary projections in half of the tumors, although only half of them exceeded 3mm, which is consistent with the study by Van Holsbeke et al., where papillary projections > 3 mm appeared in 17% of the lesions [17].

Ovarian dysgerminoma occasionally contains trophoblastic elements and produces human chorionic gonadotropin in about 5% of the cases [20]. In our study, all dysgerminomas contained a solid component and manifested minimal to moderate vascularization. The tumors were purely solid in 40% of the patients, contrary to Alcazar et al., and Guerriero et al., where dysgerminomas presented as solid tumors in 80% and 95% of the cases, respectively [1, 21]. Similarly to Alcazar et al., and Guerriero et al., we found dysgerminomas as vascularized tumors in Doppler sonography [1, 21]. However, in our study dysgerminomas manifested minimal to moderate vascularization instead of moderate to high vascularization, as was reported by these authors [1, 21]. We found papillary projections in 20% of dysgerminomas, while in the study by Guerriero et al., papillary projections appeared in 5% of the tumors [21]. There are two case

reports regarding dysgerminoma, which describe its sonographic appearance to be richly vascularized, multilocular-solid tumors [22, 23].

We described metastatic ovarian tumors, despite not measuring their hormone levels, as many papers show that metastatic tumors may have hormone-secreting stroma [4-10]. The majority of metastatic ovarian tumors with functioning stroma produce androgens, although estrogen secretion has also been reported [10]. Valentin et al., showed that metastatic tumors are mostly solid and, in the case of cystic tumors, they often do not have papillary projections [24]. Our results were different as the majority of tumors were multilocular-solid and papillary projections were found in 56% of the tumors. Purely solid masses were found only in 22% of the cases. Alcazar et al., showed that 53% of metastatic ovarian tumors are multilocular-solid [25]. In our analysis, most metastases were well-vascularized in color Doppler, with low-resistance flow, which corresponds to the findings of Alcazar et al. [25]. The divergence between studies describing ultrasonographic appearance of metastatic ovarian tumors may be partly explained by differences in the origin of metastatic tumors. As was shown in a study by Testa et al., ovarian metastases from colon, rectum, and appendix are mostly multilocular-solid, while breast cancer, stomach cancer, lymphomas and endometrial cancer occurred as solid tumors [9]. In our study, CA125 levels were elevated in the case of metastatic ovarian tumors and this finding has been confirmed by previous reports [9, 24].

In our study, fibrothecomas appeared mostly as solid tumors with minimal vascularization. Similarly, Valentin et al., Palladini et al., and Bazot et al., suggest that fibrothecomas are mostly solid tumors [26-28]. Additionally, Palladini et al., claim that theca cell tumors have predominantly minimal or moderate vasculature, which is similar to our observations [27].

In the presented study, struma ovarii occurred as small, solid tumors with high vascularization, which does not correlate with the results of Savelli et al. [29]. In their study, struma ovarii occurred most frequently as multilocular-solid tumors, with various intensification of vascularization, where moderate flow was the most frequent and appeared in 40% of the patients. In our study, there were no significant symptoms of hyperthyroidism but several authors demonstrated clinical manifestations of hyperthyroidism or goitre without hyperthyroidism [30-33].

In our study, there were no Sertoli-Leydig cell, Sertoli cell, or Leydig cell tumors. Demidov et al., reported all Leydig cell tumors and Sertoli cell tumors to be solid on ultrasound examination [34]. Leydig cell tumors were predominantly small lesions. Sertoli-Leydig cell tumors were more variable in size and they occurred mostly as solid or multilocular-solid lesions. These authors did not report papillary projections in any of these tumors. Endocrine symptoms appeared in 50-80% of Sertoli-Leydig cell tumors [35]. The most common endocrine manifestations were oligomenorrhea/amenorrhea (47%), hirsutism (27%), menstrual irregularity (20%), and deepening of the voice (7%) [34]. Endocrine manifestation is strongly associated with tumor differentiation. Clinical symptoms occur in 77% of patients with poorly differentiated tumors, in 73% with neoplasms of intermediate type, and in 25% with well-differentiated tumors [36].

Alcazar et al., reported elevated CA125 levels in most patients with dysgerminomas, while in our study median CA125 levels in dysgerminoma patients were within normal ranges. In the case of granulosa cell tumors and fibrothecomas, both our study and the study of Alcazar et al., indicated that these tumors are not associated with elevated CA125 levels [1].

Conclusions

In ultrasonographic evaluation, granulosa cell tumors occurred most frequently as large unilocular-solid or multilocular-solid cysts with moderate to high vascularization of low-resistance flow. Papillary projections were present in about 25% of the tumors. Dysgerminomas were predominantly large unilocular-solid cysts or purely solid tumors, with minimal to moderate low-resistance vascularization. Fibrothecomas were solid masses with minimal, high-resistance vascularization. Struma ovarii occurred as small, solid masses with abundant, high-resistance vascularization. Metastatic ovarian tumors presented mainly as multilocular-solid tumors with strong, low-resistance vascularization. We are of the opinion that knowing the ultrasonographic features and CA125 levels of hormonally active ovarian tumors may facilitate preoperative diagnosis of adnexal mass.

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KOMUNIKAT

Warsztaty Onkologii Ginekologicznej

Postępowanie
w nawrotach nowotworów
narządów płciowych

03-04 czerwca 2016

Poznań, Hotel HP Park, ul. abp Antoniego Baraniaka 77

Organizatorzy:

Klinika Onkologii Ginekologicznej UM w Poznaniu

Komitet naukowy

Prof. dr hab. n. med. Ewa Nowak-Markwitz

Prof. dr hab. n. med. Marek Spaczyński

T E M A T Y K A

- Nawroty stanów przedrakowych i wczesnych postaci nowotworów narządów płciowych
- Rozpoznawanie nawrotów
- Leczenie nawrotów nowotworów narządów płciowych – kiedy zakończyć terapię?

Serdecznie zapraszam

Prof. dr hab. n. med. Ewa Nowak-Markwitz

Szczegółowe informacje:

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