Intracystic evaluation of tumor markers in benign and malignant ovarian pathology

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Summary

Objective: To evaluate, in patients with benign and malignant ovarian cysts, serum samples and ovarian intracystic fluids for the presence of tumor markers such as CA 125, CA 15.3, tissue polypeptide antigen (TPA), CA 19.9 and the carcinoembryonic antigen (CEA).

Material and Method: We studied overall 64 patients with ovarian pathology. Sixteen patients were affected by functional cysts, 28 women by benign cystic tumors and 20 by cystoadenocarcinomas.

Results: Average serum levels of all but CA 15.3, TPA and CEA tumor markers of benign cystic ovarian tumors were higher than those of functional cysts. All but CA 19.9 mean intracystic fluid markers levels were more elevated in benign tumors than in functional cysts. In patients with malignant cystic tumors, all but CEA mean serum marker levels were higher than those of benign tumors; furthermore even all mean intracystic levels of markers were more elevated than those of benign tumors.

Conclusion: This study confirmed the high positivity of tumor markers such as CA 125, CA 15.3, TPA, CA 19.9 and CEA in both the serum and intracystic fluid of patients with malignant epithelial ovarian tumors.

Key words: Cystic ovarian pathology; CA 125, CA 15.3, TPA, CA 19.9 and CEA; serum and intracystic fluid evaluation.

Introduction

Tumors markers such as CA 125, CA 15.3, tissue polypeptide antigen (TPA), CA 19.9 and the carcinoembryonic antigen (CEA), which are even detected by immunohistochemistry in neoplastic tissue, can be assayed in serum of patients with malignant ovarian tumors. CA 125, as well as TPA [1], are excellent markers for monitoring the disease course in ovarian carcinoma, especially in epithelial ovarian cancer [2]. However in patients with the mucinous type the sensitivity of CA 125 is low; 58%-69% of the patients have an elevated serum CA 125 level compared with 80%-90% of those with the serous type [3, 4]. Thus, the assay of mucin-like tumor markers such as CA 19.9 and CEA is needed in order to monitor the effect of therapy in patients with mucinous ovarian cancer [5]. In fact, most patients (83%) with mucinous ovarian cancers have an elevated serum CA 19.9 level, which is higher than that determined for the mucin CA 15.3 (17%) [6].

These tumor markers have also been detected in the serum of patients with benign ovarian pathology (functional cysts, endometriosis, benign tumors, inflammatory diseases) in spite of the growing use of always more specific monoclonal antibody [7, 8].

The aim of our study was to evaluate, in patients with histopathologically verified benign and malignant ovarian cysts, serum samples and ovarian intracystic fluids for the presence of tumor markers such as CA 125, CA 15.3, TPA, CA 19.9 and CEA, which are commonly assayed in the management of gynecologic tumors.

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Patients and Methods

We studied 44 patients with age ranging from 17 to 76 years (mean 62 years), affected by cystic ovarian tumors which were benign at histology. We observed 16 (36%) functional cysts, 28 (64%) benign cystic tumors (14 mucinous cystoadenomas, 10 serous cystoadenomas and 4 cystoadenofibromas).

We even evaluated 20 cases of cystoadenocarcinomas (12 mucinous and 8 serous). The median age of these women was similar to that of women with benign ovarian pathology. According to the guidelines of the 1988 International Federation of Gynaecology and Obstetrics (FIGO) stage [9] we noted five cases in stage I, four in IIB and 11 in III.

The serum samples were collected before the cysts were handled surgically. Specimen punctures were obtained during surgery. The ovarian intracystic fluids were then stored at -20°C up to assay. The amount aspirated varied from 2 cc to 50 cc. The cut-off values in serum samples were the following: CA 125 (35 IU/ml), CA 15.3 (30 IU/ml), TPA (70 IU/ml), CA 19.9 (35 IU/ml) and CEA (5 ng/ml); any level above these was considered abnormal and positive.

In serum and cyst fluid, samples were assayed using enzyme immunoassay (Abbott Laboratories, North Chicago, IL, USA) for CA 125, CA 15.3, TPA, CA 19.9 and CEA.

The concentrations of tumor markers were correlated to histology and were tested for significant differences by ANOVA one-way single factor.

Results

Tumor marker values in the serum and tumor cysts of patients with benign and malignant ovarian pathology were compared.

Functional cysts (16 cases): serum levels of CA 125, CA 19.9 and CEA were lower than those of cut-off

values, whereas CA 15.3 and TPA were elevated and positive in 25% of cases (Table 1).

The values of markers (mean ± SD) in the cyst fluid were: CA 125 (118.3 ± 109.1 IU/ml), CA 15.3 (59.7 ± 53.2 IU/ml), TPA (732.2 ± 698.2 IU/ml), CA 19.9 (31.4 ± 27.6 IU/ml), CEA (1.3 ± 0.7 ng/ml). In the intracystic fluid CA 125 was elevated in 62.5% of cases, CA 15.3 in 50%, TPA in 75%, CA 19.9 in 37.5%, whereas CEA was not positive in any case (Table 1).

Benign cystic tumors (28 cases): Serum levels of markers were higher than those of cut-off in 15% for CA 125 and TPA, in 8.1% for CA 15.3 and CA 19.9, respectively. Serum CEA levels were always lower than cut-off value (Table 2).

The values of markers (mean ± SD) in the cyst fluid were: CA 125 (420.3 ± 221.1 IU/ml), CA 15.3 (84.1 ± 63.2 IU/ml), TPA (1228.2 ± 878.2 IU/ml), CA 19.9 (21.4 ± 14.6 IU/ml), CEA (15.3 ± 9.7 ng/ml). In the intracystic fluid CA 125 and TPA showed elevated values in 92.5% and 72.4% of cases whereas lower positivity percent values were observed for CA 15.3 (43%), CA 19.9 (22.5%) and CEA (25%).

In percentage, CA 125 and CEA intracystic fluid marker levels were more elevated in benign tumors than in functional cysts. However only CA 125 showed a statistically significant difference (Table 2.).

Malignant cystic tumors (20 cases): In patients with malignant cystic tumors, serum marker levels were higher than those of benign tumors with 80% of positivity for CA 125, 50% for CA 15.3 and TPA, 65% for CA 19.9 and 40% for CEA (Table 3).

The values of markers (mean ± SD) in the cyst fluid were: CA 125 (624.8 ± 224.1 IU/ml), CA 15.3 (112 ± 93.2 IU/ml), TPA (1415.5 ± 968.2 IU/ml), CA 19.9 (88.6 ± 44.6 IU/ml), CEA (18.8 ± 11.7 ng/ml). In intracystic fluid CA 125 and CA 19.9 showed elevated values in 92.5% of cases, whereas CA 15.3 was positive in 43% of cases, TPA in 30% and CEA in 20% (Table 3.).

With regard to a correlation between histotype and serum levels, CA 125 and CA 19.9 showed positivity in 90% and 50% of serous tumors whereas in 40% and 70% of mucinous types. In five cases of stage I, CA 125 was positive in 60%, CA 15.3 and CEA in 0%, TPA and CA 19.9 in 20%. In four cases of stage IIB, CA 125 was positive in 100%, TPA, CA 19.9 and CA 15.3 in 25% and CEA in 0%. In 11 cases of stage III, CA 125 was positive in 90.9%, CA 19.9 and TPA in 63.6%, CA 15.3 and CEA in 45.4%.

We observed no difference in the distribution of markers in the intracystic fluid with regard to the stages and histotype. Indeed no significant differences were found between all but TPA and CA 19.9 intracystic tumor marker levels in malignant ovarian tumors and benign adnexal cystic lesions

The sizes of the functional and benign cysts aspirated varied from 1 to 30 cm; malignant cysts varied from 3 to 25 cm.

Table 1. — *Mean values ± SD and percentage of positivity (pos. +) of markers in functional ovarian cysts.*

		CA 125 (IU/ml)	CA 15.3 (IU/ml)	TPA (IU/ml)	CA 19.9 (IU/ml)	CEA (ng/ml)
Mean values	Serum	16.3±6.5	18.5±5.2	45.3±23.9	18.2±6.5	2.0±1.5
	Intracyst fluid	118.3±109.1	59.7±53.2	732.2±698.2	31.4±27.6	1.3±0.7
Pos. (+)	Serum	0%	25%	25%	0%	0%
	Intracyst fluid	62.5%	50%	75%	37.5%	0%

Table 2. — *Mean values ± SD and percentage of positivity (pos. +) of markers in benign ovarian tumors.*

		CA 125 (IU/ml)	CA 15.3 (IU/ml)	TPA (IU/ml)	CA 19.9 (IU/ml)	CEA (ng/ml)
Mean values	Serum	21.7±12.4	16.9±2.5	38.3±24.9	22.0±18.5	2.0±1.5
	Intracyst fluid	420.3±221.1	84.1±63.2	1228.2±878.2	21.4±14.6	15.3±9.7
Pos. (+)	Serum	15%	8.1%	15%	8.1%	0%
	Intracyst fluid	92.5%	43.0%	72.4%	22.5%	25%

Table 3. — *Mean values ± SD and percentage of positivity (pos. +) of markers in malignant cystic ovarian tumors.*

		CA 125 (IU/ml)	CA 15.3 (IU/ml)	TPA (IU/ml)	CA 19.9 (IU/ml)	CEA (ng/ml)
Mean values	Serum	168.7±62.4	36.9±17.5	109.3±64.9	24.0±15.5	1.9±0.5
	Intracyst fluid	624.8±224.1	112.2±93.2	1415.5±968.2	88.6±44.6	18.8±11.7
Pos. (+)	Serum	80%	50%	50%	65%	40%
	Intracyst fluid	92.5%	43%	30%	92.5%	20%

Discussion

The preoperative distinction between benign and malignant ovarian cysts has a great clinical significance and several diagnostic methods have been proposed for this purpose. Transvaginal ultrasonography [10], color flow examination [11] and serum CA 125 levels each have limitations [12]. Menczer *et al.* [13] showed that the assay of intracystic fluid CA 125 levels for this distinction was inaccurate as well.

Thus we studied tumor markers such as CA 125, CA 15.3, TPA, CA 19.9 and CEA because we believe that the additional measurement of several markers may have a complementary clinically important significance. These tumor markers tested in patients with benign ovarian pathology showed a low positivity in serum specimens. Intracystic CA 19.9 positivity was lower than cut-off values both in 62.5% of functional cysts and in 77.5% of benign ovarian tumors, whereas CA 125 and CA 19.9 were elevated in four and two patients with cystic benign tumors. Only serum CA 15.3 and TPA resulted to be increased in functional cysts (both 25%); in benign ovarian tumors (8.1% and 15%, respectively). On the other hand, all markers except CA 19.9 and CEA, which were negative in functional cysts, were present in high

concentrations in the intracystic fluid of patients with functional and benign ovarian pathology.

The highest percentages of positivity in the intracystic fluid were those of CA 125 with 92.5% in both benign and malignant cystic tumors and with significant higher levels than those of functional cysts. Average serum levels of all but CA 15.3, TPA and CEA tumor markers of benign cystic ovarian tumors were higher than those of functional cysts. All but CA 19.9 mean intracystic fluid marker levels were more elevated in benign tumors than in functional cysts.

In patients with malignant cystic tumors, all but CEA mean serum marker levels were higher than those of benign tumors; furthermore even all mean intracystic levels of markers showed to be more elevated than those of benign tumors. However, as reported by others [14, 18, 19], the analysis of cyst fluid using the concentrations of tumor markers is of limited value for the differentiation of benign and malignant cystic adnexal masses.

The results reported in our series confirmed the high positivity of tumor markers such as CA 125, CA 15.3, TPA, CA 19.9 and CEA both in the serum and intracystic fluid of patients with malignant epithelial ovarian tumors, in accordance with the data of the medical literature [14, 15].

The relation between the tumor marker and histotype (especially CA 125 in serous types) and the relation between FIGO stage and determination of tumor markers (mass-dependent increase) showed a positive trend only in serum evaluation whereas no correspondence was demonstrated in intracystic assays both regarding stage and histotype.

On the basis of our data, the cystic benign ovarian pathology reported positive tumor markers in the intracystic fluid. Especially CA 125 represents the most sensible marker of malignant epithelial ovarian tumors, in particular in primitive or secondary serous forms [5].

These markers are determined in only low percentages in the serum of patients with benign pathology because they can not reach the blood circulation. Thus there is not always correspondence between high levels of tumor markers in intracystic fluid and those in serum. On the other hand, in cases of malignant tumors, the cells are released into the circulation because of the neoangiogenesis, hypervascularization of the tumor bed and the loss of the basement membrane [16]. Indeed, the lower tumor marker values in patients' serum compared to that in the tumor cyst fluid could also result from the metabolic degradation of antigens in the liver [17].

Higher serum concentrations than cut-off values may also be related to other structures such as tubal epithelium or endometrial mucosa, or concomitant inflammatory diseases which involve the peritoneum and often induce an increase in some tumor markers and in particular in TPA [7].

Further studies on larger series are necessary in order to get definitive conclusions on the utility of intracystic level assays of tumor markers in benign and malignant ovarian pathology.

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