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RESEARCH ARTICLE

Relationship between Serum Tumor Markers, CA-125, CEA, CA19-9, LDH, and βHCG with Histopathology and Age in Women with Ovarian Tumors

Nilajkumar D Bagde[1], Madhuri N Bagde[2], Zamir A Lone[1]

[1]Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Raipur, India. [2]Consultant Gynecologist, Department of Obstetrics and Gynecology, New Life Clinic, Nagpur, Maharashtra, India.

Abstract

Introduction: Ovarian tumors pose a diagnostic predicament as it is difficult to differentiate benign from malignant without a histopathology report. Appropriate tumor markers may serve as diagnostic aid to better decision making in the management of these cases. We attempted to determine the relationship between age, serum markers, and histopathological sub types of ovarian tumors to help distinguish benign from malignant tumors. **Methods:** A retrospective cross sectional study of all cases with ovarian tumors that had available histopathology reports and tumor marker levels was done at a single centre. Variables examined were age, histopathology report and serum tumor markers CA-125, CEA, CA19-9, LDH, and βHCG. **Results:** Histopathological analysis revealed 26% teratomas, 28% cystadenomas, 14% corpus luteal cysts, 26% carcinomas and 6% endometriomas. CA-125 was the only marker that was significantly raised in malignant versus benign tumors (p=0.008) and increased with increasing age. All women with raised CEA reports had teratomas, and none with cancers had a raised CEA. CA19-9, LDH and βHCG were not significantly different in benign versus malignant tumors. **Conclusions:** CA-125 may be used as an adjuvant diagnostic tool for ovarian cancer in older women. The role of CEA as a marker for teratomas needs further evaluation.

Keywords: Tumor markers- ovarian tumors- pathology- CA-125- CEA- Ovarian cancer- gynecologic oncology

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Introduction

As we march forward in the twenty first century, newer health challenges confront health care providers with the focus of mortality shifting from infectious diseases to malignancy. Ovarian cancer accounts for 3.4% of all new cancers and 4.4% of worldwide cancer deaths in females [1]. Screening for ovarian tumors is still limited despite this disease fulfilling the WHO criteria of improved survival if detected early [2]. The role of tumor markers has not been sufficiently investigated and more research is needed in this direction. In this study we attempt to determine the utility of the current serum markers for having predilection for a particular histologic tumor subtype and their ability to differentiate benign from malignant disease with the hope to provide a contribution towards developing better screening modalities for this lethal disease.

Materials and Methods

A search of case files of all women admitted with a diagnosis of ovarian tumors in the Obstetrics and Gynecology department between December 2016 to December 2019 was made after approval of the study from the institutional ethical committee.

All women that underwent a surgical procedure for ovarian tumor were included in the study irrespective of age. Women in whom histopathological reports were not available and women in whom surgery and histopathology failed to reveal an ovarian tumor were excluded from the study.

Corresponding Author:
Dr. Nilajkumar D Bagde
Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Raipur, India.
Email: mailnilaj@gmail.com

Data was collected for the indicators like age, histopathology reports and serum markers: Carbohydrate Antigen 125 (CA-125), Carcino Embryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA19-9), Lactate Dehydrogenase (LDH), and Human Chorionic Gonadotropin beta subunit (βHCG) levels.

The normal range of serum markers was followed as per those provided by a single testing lab. Anything above the normal range was considered raised. The reference levels used were as mentioned in Table 1 (Table 1).

Comparison was made between age, histopathology reports and serum markers. Chi square test, Chi square likelihood ratio and Pearson's correlation coefficient were used for analysis on Stata 64.

Results

Total 67 cases of ovarian tumors were operated during this time period. Data for histopathology was available for 50 women that were included in the analysis. The youngest patient was 12 years and oldest 74 years with a mean age of 38.48 + 14.93 years. 10 % females were less than 18 years, 64% between 18 to 45 years and 26% more than 45 years of age.

Histopathology analysis

Analysis of histopathology data revealed 26% tumors as teratomas, 28% cystadenomas, 14% corpus luteal cysts, 26% carcinomas and 6% endometriomas. 74% tumors were benign. No malignancies were reported in cases below 18 years (Table 2).

An age wise analysis of tumor pathology revealed 80% women below 18 years, 21.85% between18-45 and 15.38% more than 45 years of age had teratomas. Cystadenomas were found in 20% women below 18 years, 37.5% between 18-45 years and 7.69% above 45 years. Corpus luteal cysts were seen in 18.75% women between 18-45 years and 7.69% above 45 years and 12.5% between 18-45 years and 69.23% above 45 years had a carcinoma. Endometriomas were seen in 9.37% women between 18-45 years. This was the only age category that had endometriomas. In women between 18-45 years, 12.5% cases were carcinomas and 69.23% of those >45 years had carcinomas. Significantly higher number of carcinomas were seen with increasing age across all three categories (likelihood ratio chi square, p= 0.001).

Table 1. Normal Reference Range of Various Serum Markers

Marker	Normal range
CA-125*	35 U /ml
CEA†	< 2.5 ng /ml
CA19-9‡	1.20-30.9 U /ml
LDH§	100-190 U /L
βHCG‖	< 5.3 mIU /ml

*CA-125, Carbohydrate antigen 125; †CEA, Carcino embryonic antigen; ‡CA19-9, carbohydrate antigen 19-9; §LDH, Lactate dehydrogenase; ||βHCG, Beta subunit Human chorionic gonadotropin beta subunit (βHCG).

Analysis of tumor markers (Table 3)

CA-125

CA-125 and histopathology data was available in 42 women. 18 out of these 42 women (42.86%) had raised CA-125 levels. Of these 11.90 % were below 18 years, 59.52% between 18 to 45 years and 28.57% above 45 years of age. All below the age of 18years had normal CA-125 levels. Of 25 women between 18 to 45 years, 40% had raised CA-125 levels and 66.66% above 45 years had raised CA-125 levels. CA-125 levels were significantly higher in women with increasing age (likelihood ratio Chi 2, p = 0.015).

Of ten women with teratomas, nine (90%) had normal CA-125. 20% of those with cystadenomas, 66.66% with corpus luteal cyst, 75% with carcinomas and all with endometriomas had a raised CA-125. 75% women with malignancies had a raised CA-125 compared to 30% with benign conditions which was statistically significant (p = 0.008).

CEA

Of the 29 women in whom CEA reports were available, 3.45% were in the age <18 years, 68.97% were 18 to 45 years and 27.59% were >45 years of age. 6.90% of these women had raised CEA levels, all of these had teratomas. The age wise analysis showed that 5% in age 18-45 years and 12.50% above 45 years had raised CEA. None of women with cancer had raised CEA levels. There was no significant difference in CEA levels across age.

CA19-9

CA19-9 was raised in 30% women of the total 20 reports available. All of these women were in the age 18-45 years. CA19-9 was raised in 66.66 % women with teratomas, 50% women with corpus luteal cyst, 12.50% in women with malignancy and all women with endometriomas. There was no significant difference in CA19-9 levels in malignancies as compared to benign ovarian conditions (p= 0.16).

Table 2. Histopathology of Tumors in Various Age Categories

Age category	Histopathology (numbers are percentages)				
	Teratoma	Cystadenoma	Corpus luteal cyst	Clear cell carcinoma	Endometriotic cyst
<18 years	30.76	7.14	0	0	0
18-45 years	53.84	85.71	85.71	30.76	100
>45 years	15.38	7.14	14.28	69.23	0

Table 3. Tumor Markers by Malignant or Benign Histopathology Reports

Marker		Benign	Malignant
CA-125*	Normal	70%	25%
	Raised	30%	75%
CEA†	Normal	90%	100%
	Raised	10%	0
CA19-9‡	Normal	58.33%	87.50%
	Raised	41.66%	12.50%
LDH§	Normal	65%	57.14%
	Raised	35%	42.85%
βHCG‖	Normal	90.46%	85.71%
	Raised	9.52%	14.28%

*CA-125, Carbohydrate antigen 125; †CEA, Carcino embryonic antigen; ‡CA19-9, carbohydrate antigen 19-9; §LDH, Lactate dehydrogenase; ||βHCG, Beta subunit Human chorionic gonadotropin beta subunit (βHCG).

LDH

LDH levels were available in 27 women, of these 37.04% had raised LDH. LDH was raised in 66.66% women <18 years, 31.25% women between 18-45 and 37.50% >45 years. LDH levels did not show any significant difference across age groups (r = - 0.31).

LDH was raised in 33.33 % women with teratomas, 50% women with cystadenomas, none with corpus luteal cysts, 42.85% with malignancies and 33.33% with endometriomas. There was no difference in LDH levels in malignant versus benign tumors (p = 0.71).

βHCG

βHCG levels were available for 28 women of which 14.29 % were <18 years, 60.71% were 18-45 years and 25% were >45years of age. βHCG was raised in 10.71% women. Of these 33.33% had carcinomas, 33.33% had teratomas and rest had corpus luteal cyst. There was no significant difference in βHCG values across ages of malignant versus benign (p = 0.72).

Discussion

Carbohydrate antigen 125 (CA- 125) has been used as a prognostic indicator in women with ovarian clear cell cancers [3]. CA -125 levels are increased when there is tumor invasion, destruction of tissue and inflammation caused by malignancy [4]. Pre-treatment CA-125 levels are not useful to predict clinical outcome [3]. A risk of malignancy index combining CA-125, clinical features, ultrasound and menopausal status was used to distinguish malignant from benign tumors. A CA-125 more than 30 U/ml had a sensitivity of 81% and specificity of 75% in predicting malignancy [5]. However, in another study, only 27% women positive for ultrasound and CA-125 had stage one disease, so it may not be a useful screening tool for early stage cancers [6]. In our study, CA-125 was significantly higher in malignancies compared to benign disease and was found to show a significant increase with age. All women with endometriomas had a raised CA-125, so a cautious approach is suggested before using it as a sole marker for malignancy. We feel that it may prove as a valuable screening tool for detecting carcinomas in women in the later ages, > 45 years.

CA19-9 or carbohydrate antigen 19-9, also called cancer antigen 19-9 or sialylated Lewis a antigen [7] is mainly used as a marker and additional diagnostic tool for pancreatic cancer [7-8]. It has also been found to be raised in ovarian cancers [9] and a combination of CA19-9 with CA-125 was demonstrated to have a high diagnostic efficacy for prediction of mucinous ovarian cancers [10]. The levels were also raised in dermoid cysts [11-12] and correlated with the average diameter and weight of the tumor [11-13]. Considering its low specificity, its use as a marker for malignancy was considered limited [14].

In our analysis 66.66% of teratomas and all endometriomas had a raised CA19-9 whereas only 12.5% cancers had a raised CA19-9. So its role as a diagnostic tool for malignancy appears to be restricted.

CEA or carcino embryonic antigen is a fetal glycoprotein first isolated from colorectal cancer tissue (14). CEA alone or in combination with other markers (CA125 + CEA + CA19-9 and CA125 + CEA + CA19-9 +AFP and CA125 + CA15-3) did not show any difference in distinguishing benign from malignant lesions [15]. A similar conclusion was proposed by Sagi-Dain et al (2015), but they also suggested that higher CEA levels may be useful to distinguish between primary ovarian cancers versus metastatic tumors.

All our patients with raised CEA levels had teratomas. Hitchins et al (1989) reported raised CEA levels in eight of 36 with mature differentiated teratoma compared with one of 39 patients without teratoma [16]. However the levels remained elevated post complete tumor resection suggesting role of other confounders like hepatotoxicity from chemotherapy, intercurrent disease or other unknown factors. In our study CEA was positive in 40% women with teratoma and teratoma was the only tumor with a positive CEA report. Hence we propose further research to ascertain its value as a tumor marker for teratomas.

Lactate dehydrogenase is an enzyme of the glycolytic pathway. Mixed reports are available regarding this enzyme activity in ovarian tumors. LDH was reported to be raised in malignant primary [17-19] and secondary [19] ovarian tumors, with no difference with regards to histological subtypes [18-19]. High LDH levels have been associated with ovarian and extragonadal dysgerminomas [20-23]. However, older studies did not report a significant association between LDH and ovarian tumors [24]. The literature suggests that LDH may be of potential use as a tumor marker in ovarian dysgerminomas and higher stage ovarian cancers but our results fail to support this claim.

βHCG overexpression in cells lead to increased tumor formation and growth by increasing cell cycle progression and decreasing apoptosis [25] and also leads to increased expression of epithelial mesenchymal transition markers in ovarian cancer cell lines facilitating their migration and invasion [26]. Serum beta subunit of HCG or beta core fragment formed by degradation of HCG is produced in

68% of ovarian cancers [27] and is related to the grade and stage of tumor [28]. However the results have not been reproducible and Djurdjevic et al (2011) did not find HCG of any diagnostic value nor having any relation to FIGO stage of ovarian cancers [29].

Fifteen different forms of HCG have been identified and the regular HCG, free βsubunit (free βHCG), hyper glycosylated HCG (H-HCG), hyper glycosylated chorionic gonadotropin β subunit (H- HCGβ), free alpha subunit (αHCG) and O-glycosylated alpha subunit (O-HCGα) are produced by non-trophoblastic cancer cells and the hyper glycosylated beta subunit correlates with stage and grade of cancer [30].

In our study βHCG was more often raised in benign tumors than malignant but the difference was not significant. A more specific test targeted towards specific type and subunit may provide more insights about the use of this molecule as a serum marker for malignancy.

In conclusions, serum tumor markers for ovarian cancers may provide insights towards early detection of this grave malignancy. CA 125 is a promising marker that may be used for early detection of ovarian cancers in later ages. The role of CEA as a diagnostic tool for teratomas needs further evaluation. CA19-9, LDH, and βHCG did not show any significant correlation with malignancies in our study.

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