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THE CLINICOPATHOLOGICAL SIGNIFICANCE OF PREOPERATIVE SERUM CA125 LEVELS IN DIAGNOSING BENIGN AND MALIGNANT OVARIAN TUMOURS

Pathology

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ABSTRACT

Introduction: The serum CA125 level is found to be most useful tumor marker in diagnosis of ovarian tumours. **Objective:** The aim of the present study was to evaluate preoperatively CA125 levels in suspected ovarian tumours, and compare it. **Materials and methods:** 100 ovarian tumour cases was included in the study. Preoperative serum CA125 levels were measured. Histopathological diagnosis was made and the tumours were categorized into Benign, Borderline and Malignant. CA 125 levels were compared. **Results:** Among the 100 ovarian tumour cases, the majority were benign comprising of 76 cases (76%), 3 (3%) were borderline and 21 (21%) malignant. The mean CA 125 levels of benign, borderline and malignant tumours were found to be 23.63 ± 14.74 , 130 ± 28.28 and 302.17 ± 193.42 respectively with p value of <0.0001. **Conclusion:** Significant correlation was found between benign and malignant groups with p value < 0.0001. It serves as valuable tool as early diagnostic & prognostic marker.

KEYWORDS

CA 125, Ovarian tumours

INTRODUCTION:

The discovery of OC125, was made by Bob Bast1 and his colleagues in 1981, an antibody that recognizes CA125.

Cancer antigen 125 (CA125), also called as mucin-16 (MUC16), is the most widely used tumour marker in ovarian cancer and considered the "gold standard" specifically in ovarian neoplasm1,2. Recognition of CA125 as a circulating antigen opened the door to biomarker research for ovarian carcinoma, now potentially clinically significant and a flourishing field. CA125 is expressed as a membrane-bound protein at the surface of cells that undergo metaplastic differentiation into a Müllerian-type epithelium or released in soluble form in bodily fluids[2,3].

CA125 AS A BIOMARKER FOR OVARIAN CANCER[2]

Ovarian cancer is found to be a second most common and the most lethal gynecologic malignancy. Epithelial ovarian cancer constitutes majority of malignant ovarian tumors in adult women. The serum CA125 level is found to be most useful tumor marker in diagnosis of ovarian cancer and the detection of recurrence after primary treatment, and its value has been demonstrated as a marker for patient prognosis, disease progression, and response to chemotherapy. The epithelial surface of the normal ovary do not show positivity for CA125 staining but cells lining ovarian cysts as well as papillary excrescences within ovarian cysts often show positive[4].

AIM:

1. To evaluate serum CA125 levels preoperatively in all the suspected cases of ovarian tumours based on clinical examination and radiological findings.
2. Compare serum CA125 levels in benign, Borderline and malignant ovarian tumours.

MATERIALS AND METHODS:

The present study was done prospectively on 100 cases of suspected ovarian tumours based on clinical examination and radiological findings. Present study was done for a period of one year in Department of pathology at our institute.

The needed clinical details were archieved from the respective departments. The cases were selected based on inclusion/exclusion criteria. All the cases suspected clinically and radiologically diagnosed as ovarian tumors were included in the study after obtaining the consent from the patients.

Whole blood samples were obtained preoperatively from a peripheral vein from patients with a pelvic mass considered to be an ovarian tumor by clinical examination. Preoperative serum serum CA125 levels were measured using the ELFA method by Mini VIDAS instrument. The histopathologic investigations were performed or confirmed by senior pathologists later. All the tumours were categorized on histopathology into Benign, Borderline and Malignant tumours. CA 125 levels were compared with benign, borderline and malignant groups.

Data analysis:

Statistical analysis was done on the basis of the objectives stated. Data were collected and entered in Microsoft Excel 2007 and analysis was done using SPSS version 16. The data were analysed and tabulated as percentages, mean, standard deviation. The sensitivity, specificity, positive and negative predictive values along with the accuracy were calculated. Chi –square test and Post hoc test was also done to know the differences between the benign, borderline and malignant groups. P < 0.0001 was taken as statistically significant.

RESULTS:

The present prospective study was done on 100 ovarian tumours. In our study, 66 patients with ovarian tumours showed a serum CA 125 value of less than or equal to 35 IU/ml and 34 patients showed a CA 125 value of more than 35 IU/ml as depicted in table 1. Cut off level of serum CA125 was taken to be 35 U/mL according to Bast et al[1].

Table 1: CA 125 values among the ovarian tumours

Serum CA 125 (IU/ml)	Total (100)	Chi Square	P Value
≤ 35	66	58.00	< 0.0001
> 35	34		

The ovarian tumours were categorized based on histological findings. Among the 100 ovarian tumour cases in the present study, the majority were found to be benign comprising of 76 cases (76%), 3 (3%) were found to be borderline and 21 (21%) were found to be malignant on histopathology as depicted in table 2.

Table 2. Distribution of benign, borderline and malignant cases based on histopathology.

TYPE OF TUMOURS	NUMBER OF CASES	PERCENTAGE (%)
Benign	76	76 %
Borderline	3	3%
Malignant	21	21 %
TOTAL	100	100 %

Of 100 cases of ovarian tumours, 76 (76 %) were of surface epithelial origin, 8(8%) were of germ cell tumours, 8(8%) were of non neoplastic cyst/ tumour like lesions ,5(5%) were of sex cord-stromal tumours, 1 (1%) case was of mixed-sex cord stromal tumour, 1(1%) case was of metastatic origin and 1(1%) case was of torsion of benign cyst as

shown in table 3.

Table 3. Distribution of type of ovarian tumours on histopathology

TYPE OF TUMOUR	TOTAL CASES	PERCENTAGE %
Surface epithelial tumours	76	76
Sex- cord stromal tumours	5	5
Mixed sex cord stromal tumours	1	1
Germ cell tumours	8	8
Metastatic tumours	1	1
Tumour-like lesions/ Non-neoplastic cysts	8	8
Torsion of benign cyst	1	1
TOTAL	100	100

The mean CA 125 levels of benign, borderline and malignant tumours were found to be 23.63 ± 14.74 , 130 ± 28.28 and 302.17 ± 193.42 respectively with p value of <0.0001 as shown in table 4.

Table 4: Mean serum CA 125 levels in benign, borderline and malignant ovarian neoplasms.

Sl. No.	Nature of ovarian neoplasm	Serum ca 125 levels Mean ± SD	P-Value
1.	Benign	23.63 ± 14.74	<0.0001
2.	Borderline	130 ± 28.28	
3.	Malignant	302.17 ± 193.42	

Total of 66 cases of benign tumours showed CA 125 level ≤ 35 IU/ml as shown in table 1. Majority of benign tumours in descending order included serous cystadenoma(32), mucinous cystadenoma(14), mature cystic teratoma(6), corpus luteal cyst(3) , follicular cyst(5), endometriotic cyst (3), fibroma(1) , fibrothecoma(1) and ovarian torsion cyst(1). All had a range from 10-35 IU/ml with exceptional to 10 following cases. 10 of the tumours showed CA 125 value of more than 35 IU/ml i.e, endometriotic cyst (35.2-48 IU/ml in 7 cases), followed by fibrothecoma (40 IU/ml and 45 IU/ml in 2 cases) followed by one case of benign Brenner tumor (90 IU/ml).

All the 3 cases of the borderline tumor showed a CA 125 value of more than 35 IU/ml i.e (2 cases of the borderline mucinous tumor had 70 IU/ml and 110 IU/ml respectively) while one case of the borderline serous tumour had 150 IU/ml.

All the 21 malignant tumours showed a CA 125 value of more than 35 IU/ml i.e, highest was seen in one case of endometrioid carcinoma (900 IU/ml) and lowest was seen in the metastatic tumor (one case, 60 IU/ml) .Among the serous cystadenocarcinoma range was 122-571 IU/ml. Mucinous carcinoma showed range from 200-400 IU/ml. One case of yolk sac tumor showed 52 IU/ml, one case of granulosa cell tumor showed 200 IU/ml, One case of sertoli leydig cell tumor showed 150 IU/ml. One case of dysgerminoma had 154 IU/ml.

In the present study, the sensitivity, specificity, PPV and NPV of serum CA 125 in diagnosing malignant ovarian tumours with a cut off of 35 IU/ml was 100%, 86.8%, 67.7% and 100%. The diagnostic accuracy was 89.6%.

There is a significant correlation found between the benign and malignant groups with a p value < 0.0001. There was no statistically significant association observed between benign and borderline group (p =0.2213) and also between the borderline and malignant group (p = 0.0274) as depicted in table 5. This indicates CA125 levels can be elevated in some benign conditions like endometriosis, whereas borderline tumours can show a normal or slight increase in the CA 125 levels, whereas malignant cases almost always shows increased CA125 levels.

Table 5: Turkeys post hoc test was done to find out the difference between the benign, borderline and malignant groups.

S. No	Post turkeys test	95 %Confidence interval	P-Value
1	Benign VS Borderline	-45.0797 to 257.8197	0.2213
2	Benign VS Malignant	226.4837 to 330.5963	<0.0001
3	Borderline VS Malignant	15.6916 to 328.6484	0.0274

DISCUSSION:

The present study concentrated on the ability of CA 125 to distinguish between benign and malignant ovarian tumours..

The serum CA125 values in the present study was ≤35 IU/ml in 66% and > 35 IU/ml in 34 %. Kim C et al5 also observed CA 125 < 35 IU/ml in 70% and> 35 IU/ml in 33% of his cases.

The mean serum CA 125 levels in benign, borderline and malignant tumours were 23.63 ± 14.74, 130 ± 28.28 and 302.17 ± 193.42 respectively. Kim C et al5, observed mean values in benign, borderline and malignant ovarian tumors as 41.99 ± 67.03, 105.76 ± 141.83 and 206.01 ± 187.02 respectively.

Increased serum CA 125 levels was predominantly observed in 10 % of benign cases, 3% of borderline tumours and all the 21% of the malignant tumours in our study.

In the present study, Serum CA 125 levels < 35 IU/ml was seen in 66 cases of benign lesions , majority of them being serous cystadenoma. Increased serum CA 125(>35IU/ml) was predominantly observed in 10 cases of benign tumours. Among the 10 cases, endometriotic cyst had a significant rise of preoperative serum CA 125 levels followed by fibrothecoma, one benign brenner tumour which was in accordance with the study done by Kim C et al5 , who observed increase in serum CA125 levels commonly in 30.1% endometrioitic cyst (76.07 U/mL) followed by 11.8% in serous cystadenoma (42.2 IU/ml) and in 0.7% fibrothecoma (43.37IU/ml).

In the present study, borderline tumours (3%) showed a moderate rise in serum CA 125 levels (range 70 - 150 IU/ml). Borderline serous tumours showed marked raised in serum CA125 levels i.e, compared to borderline mucinous tumours. Similarly Gultekin et al6, observed increase in the mean serum CA 125 levels in borderline serous tumour (172 IU/ml) compared to borderline mucinous tumour (39 IU/ml). Kim C et al5 ,also observed preoperative CA 125 level was higher in serous type (144.38 U/mL) than mucinous type (82.59 U/mL) which was similar to our study.

In the present study all the 21 cases of the malignant cases showed increase in CA 125 values of > 35 IU/ml. Among them endometrioid carcinoma had highest CA125 value followed by serous cystadenocarcinoma and mucinous cystadenocarcinoma. According to Thakur V et al7, mean serum CA125 concentration in serous adenocarcinoma (1571± 121.5) was much higher than mucinous tumour(775 ±78 U/ml). Endometrioid carcinoma was very high (2853 ± 136 U/ml) compared to our study. In a study done by Manish Kumar Das et al8 , he observed highest level of rise of tumour marker in serous cystadenocarcinoma (>500IU/ml) followed by mucinous cystadenocarcinomas and endometrioid carcinomas (range 100 -500 IU /ml) which was comparable to our study.

In the present study, the sensitivity , specificity, PPV and NPV of serum CA 125 in diagnosing malignant ovarian tumours with a cut off of 35 IU/ml was 100%, 86.8% ,67.7% and 100%. The diagnostic accuracy was 89.6%. The study done by Agrawal et al9 also showed sensitivity of 90.9%, specificity of 40% with diagnostic accuracy of 81.5%.

The p value (< 0.0001) was found to be significant between the benign and malignant group of tumours indicating its strong ability to distinguish benign from malignant category. Kim C et al 9also observed p < 0.001 in his study. However, there was no statistical significant association between benign and borderline group of tumours (p = 0.2213) and also between borderline and malignant groups (p= 0.0274) in present study. There were 3 cases of borderline ovarian tumours which had significant increase in serum CA 125 levels which could not be clubbed either with benign or malignant cases, as there was increased serum CA 125 levels in some benign cases as well.

However Owing to the heterogeneity of its distribution, an elevated CA 125 value must be interpreted with great caution in the context of the clinical scenario and indication for which it is being tested as it is also found to be elevated in some acute pancreatitis, non ovarian tumours like colorectal carcinomas and squamous cell carcinomas10. An important aspect to highlight is the ability of CA125 to be in the normal range after surgical excision of the tumor; this role assigns it as a preferred marker for follow-up of borderline tumors and in generally of ovarian tumors[11].

CONCLUSION :

CA 125 has the ability to distinguish malignant from benign ovarian tumours. The ability to predict whether a tumour is malignant or

benign before surgery is important in deciding the extent of surgery, and the use of frozen sections may help in this distinction.

CA125 level is a well established sensitive tumour marker with high accuracy in the diagnosis of malignant ovarian cancer. Its level of > 35 U/ml is a useful preoperative test in diagnosing malignant from the benign ovarian lesions.

Although the histopathological diagnosis remains the gold standard technique, CA 125 levels accompanied with intraoperative diagnostic procedures can be used as a valuable tool in determining the extent of surgeries and as early prognostic marker.

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