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Original Research Article

Clinico-pathological correlation of ovarian tumors and tumor like lesions with role of CA125 and HE4 as biomarkers for discrimination of benign and malignant ovarian tumors

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ABSTRACT

Background: Ovarian tumors and tumor like lesions of ovary frequently form pelvic masses and are associated with hormonal manifestations. Clinically or surgically they can mimic malignancy but pathologically they could be benign tumors or tumor like lesions.
Methods: The aim of present study is to do clinico-histopathological correlation of ovarian tumors and tumor like lesions of ovary and also evaluate the role of serum CA125, HE4 and calculate risk of ovarian malignancy algorithm (ROMA), for differentiation of benign and malignant ovarian tumors.233 cases of ovarian tumors and tumor like lesions were studied. Tumors were classified according to WHO classification. Clinical and histological findings were compiled on proforma and subjected to analysis.
Results: In present study, out of total 233 cases, 41.2% were ovarian tumors and 58.8% tumor like lesions of ovary. Among tumor like lesions, follicular cyst was commonest lesion while among ovarian tumors, benign serous surface epithelial tumor was commonest. In patients with ovarian tumors, blood samples were collected, before and after the treatment for analysis of CA125, HE4 and ROMA.
Conclusions: Serum values of CA125and HE4 as well as ROMA were highly elevated in women with malignant epithelial tumors as compared to women with benign lesions. Also, all the parameters i.e. HE4, CA125 and ROMA showed significant difference before and after surgery. Hence measuring serum HE4 and CA125 along with ROMA calculation may provide higher accuracy for detecting malignant epithelial ovarian tumor.

Keywords: Clinico-histopathological, CA125, HE4, ROMA

INTRODUCTION

Ovarian tumour and non-neoplastic lesions present a great challenge to gynecological oncologist. Certain non-neoplastic lesions of the ovary frequently form a pelvic mass and potentially mimic an ovarian neoplasm. Their proper recognition and classification is therefore important to allow appropriate therapy. Ovarian cancer is the seventh leading cause of cancer death (age standardized mortality rate: 4/100,000) among women worldwide and in India it's comprising up to 8.7% of cancers in different parts of the country. Variable histopathological presentations of ovarian tumours lead to detection in advanced stage where neither effective surgery nor chemotherapy can be done.[1]

Early diagnosis is difficult due to its asymptomatic nature, inaccessible site and the limited use of various new techniques like cytology and biopsy. Thus, ovarian neoplasm offers a good field for research.[1]

Therefore, the role of tumor markers to further characterize the ovarian mass has come into clinical use.[2] Carbohydrate antigen 125 (CA125) is the most widely used tumor marker in ovarian cancer; however, its predictive power is far from ideal.[2]

It is elevated in about 80% of women with epithelial ovarian cancer (EOC) but only in 50% of women with early stage disease.[2] The specificity of CA125 is limited, since it can be elevated in a range of common benign gynecologic or non-gynecologic conditions.[3]

Furthermore, the sensitivity and specificity of CA125 are not high enough for population screening for the detection of early stage ovarian cancer.[4] Therefore, the identification of new cancer biomarkers to replace or complement CA125 is urgently needed and to improve its sensitivity for early detection, human epididymis protein 4 (HE4) has been investigated.[5] HE4 is primarily expressed in the reproductive and respiratory tracts and is overexpressed in ovarian cancer cells, especially in histologic subtypes of serous or endometriod carcinoma and it has been suggested to be a serological marker of ovarian cancer.[5]

In this study, we aimed to compare the characteristics of HE4 and CA125 in epithelial ovarian cancer and benign gynecological diseases, and to evaluate the diagnostic performance of both CA125 and HE4 in discriminating ovarian cancer from other benign gynecologic diseases. In the view of diagnostic utility and the prognostic significance of provided tools, the present study will be performed with the following aims and objectives.

- Clinicopathological correlation with histological subtypes of ovarian tumors and tumor like lesions.
- To find out the spectrum of ovarian tumors and tumor like lesions in Lala Lajpat Rai Memorial Medical College, Meerut.
- To evaluate and compare the role of HE4 and CA125 as biomarkers for discrimination of benign and malignant ovarian tumors with special reference to surface epithelial tumors.

METHODS

In this study, patients attending the outpatient and inpatient department of Obstetrics and Gynecology of SVBP Hospital attached to LLRM Medical College, Meerut will be studied over a period of one year. A detailed clinical history, physical examination and laboratory examination of all the cases was done.

Material

Peripheral blood collection

An 5ml of blood was collected before and after the surgery in plain vial (for CA125 and HE4 measurements) centrifuge-blood samples immediately centrifuged at around 3000 rpm for 10 minutes at 40C. Supernatant serum is collected and sent for CA125 and HE4 measurements by outsourcing method. Post operatively removed ovary kept in formalin with proper labelling and sent for histopathological examination to pathology department of LLRM Medical College, Meerut.

Procedure

After explaining the aim of the study to the subjects and after obtaining their written consent and ensuring about the confidentiality of their personal information, 5ml of blood was collected from patients a day before surgery. Blood samples were immediately centrifuged at around 3000 rpm for 10 minutes at 40C; The supernatant serum was collected and kept at -700C up to the time when the study populations HE4, CA125 and ROMA were tested. Sampling intervals and freezing were at a maximum of one hour. After determining the serum values of HE4 and CA125, ROMA was calculated using the two tumor markers. Measurement of the series of CA125 and HE4 values were performed using chemiluminescent enzyme immunoassay. ROMA was calculated based on following formula.

Pre-menopausal:

Predictive Index (PI) = 12+2.83 LN (HE4) + 0.626×LN (CA125)

Post menopausal:

Predictive index (PI) = 8.09+1.04×LN (HE4) + 0.732×LN (CA125).

$$Predictive\ Probability\ (PP) = \frac{Exp.(PI)}{1 + Exp.(PI)} \times 100 = ROMA\ (\%)$$

Cut off values of CA125 and HE4 were 35μ/ml and 70 pm respectively based on the study of Nolen et al.[7] ROMA cut off for patients with high risk of ovarian cancer in premenopausal women were considered as ≥13.1% and for post-menopausal women as ≥27.7 % based on the study conducted by Moore et al.[8] Based on ROMA results subjects were differentiated into low risk and high risk groups. Data from this present study was gathered using the following methods; descriptive statistics (mean ±SD), fisher exact test and chi-square tests. Statistical analyses were performed using SPSS 19 with normal results. Distribution of data was evaluated with the use of Kolmogorov-Smirnov test. P value of <0.05 was considered statistically significant

RESULTS

As evident from Table 1, out of 233 cases, ovarian tumors comprised, 96 cases (41.2%), while tumor like lesions of ovary comprised, 137 cases (58.8%) (Table 1).

Table 1: Distribution of ovarian tumors and tumor like lesions (N=233).

Distribution	No. of cases	%
Ovarian tumors	96	41.2
Tumor like lesions	137	58.8
Total	233	100

Table 2: Distribution of different tumor like lesions of ovary (N=137).

Tumor like lesions	No. of cases	%
Follicular cyst	102	74.6
Corpus luteal cyst	27	20
Endometriosis	04	2.7
Inclusion cyst	04	2.7
Total	137	100

Table 3: Distribution of ovarian tumors (N=96).

Types of tumor	No.	%
Surface epithelial tumors	67	69.8
Germ cell tumors	23	23.9
Sex cord stromal cell tumors	06	6.3
Total	96	100

Table 4: Serum CA125, HE4 and ROMA values in ovarian tumors (N=96).

Tumor	CA125 median (u/ml)	HE4 median (pmol/l)	ROMA (%)
Benign			
Cystadenoma/ Cystadenofibroma	12.6	53	8.4
Fibroma/thecoma	30	48	7.1
Mature teratoma	24	47	6.7
Malignant			
Epithelial ovarian carcinoma	558	238	80.5
Metastatic tumors	785	184	80.6

As evident from Table 2, out of total 137 cases of tumor like lesions, most common is follicular cyst, 102cases (74.6%) followed by corpus luteal cyst, 27 cases (20%) and endometriosis, inclusion cyst each with 4 cases (2.7%).

Table 3 shows distribution of ovarian tumors according to WHO classification (2014), in which surface epithelial tumors were the commonest, 67 cases (69.8%), followed by germ cell tumors, 23 cases (23.9%) and sex cord stromal cell tumors, 6 cases (6.3%).

There was significant difference in HE4 and CA125 values between the ovarian cancer group (median 441U/ml, for CA125, and median 240pmol/l, for HE4) than the benign gynecological disease (median 24U/ml, p = 0.001 for CA125, and median 47pmol/l, p = 0.001 for HE4) (Table 4 and 5).

Table 5: Level of HE4 and CA125 in ovarian cancer group before and after treatment (N=96).

	Before treatment Median (range)	After treatment Median (range)	P values
CA125	441 (212-1422)	30 (21-39)	<0.001
HE4	240 (184-782)	103 (92-144)	<0.001
ROMA	80.6 (77.8-98.7)	31.9 (26-51.4)	<0.001

DISCUSSION

Table 6 shows different ovarian tumors comparision in % in various studies. Among the individual tumors, the commonest benign epithelial tumor was serous cystadenoma (50%), followed by mucinous cystadenoma (07%). Among malignant epithelial tumors, serous cystadenocarcinoma (4.1%) was the most common, followed by Mucinous cystadenocarcinoma (%). Similar findings were seen in studies by Maheshwari et al and Gupta et al.[11,12]

This study accounted for 50.1% cases of serous cystadenoma which is comparable to studies by Misra et al and Maheshwari et al who reported incidence of serous cystadenoma, that is, 49% and 46.01%, respectively.[13,11]

Mucinous cystadenoma accounted for 7.3% cases of neoplastic lesions. Higher incidence have been reported by Prabhakar et al, (18%) and Maheshwari et al, (13%).[14,11] 3.0% cases of mucinous cystdenocarcinoma were reported in present study, while Maheshwari et al, Pilli et al and Prabhakar et al showed an incidence of 0.25%, 4%, and 5% respectively.[11,9,14]

There were 3.2% cases of granulosa cell tumor and it was slightly more compared to the study done by Ramachandra et al.[15] Mature cystic teratoma, most common germ cell tumour, accounted 18.7% of total neoplastic lesions. Studies by Tyagi et al, Gupta et al and Couto et al which showed an incidence of 18.46%, 23.13% and 15.45% respectively.[16,12,17]

Table 6: Comparison of frequency of different ovarian tumors with other studies.

Ovarian tumors	Pilli et al[8]	Bodal VK et al[9]	Kanthikar et al[1]	Present study
Surface epithelial tumors	70.9	71.7	67.14	67
GCT	21.2	23.3	22.8	23
Sex cord stromal tumor	6.7	3.34	5.7	06

Table 7: Comparision of serum markers and ROMA values with other studies.

Senstivity	Hamed et al[17]	Terlikowaska et al[15]	Present study
HE4	90%	84.1%	90%
CA125	83.3%	83.1%	85%
ROMA	96.7%	86.2%	97%
Specificity			
HE4	95%	86.3%	96%
CA125	85%	82.4%	75%
ROMA	80%	86.8%	99.8%

Table 7 shows comparisons of serum marker n ROMA values in various studies. In this study, we investigated the role of HE4 alone and in combination with CA125 in assessing patients with epithelial ovarian cancer. Results of HE4 testing confirm the high sensitivity and specificity of this molecule over CA125 for epithelial ovarian carcinomas (sensitivity 90% vs. 85% and specificity 96% vs.75%) respectively.

In assessment of treatment response, both CA125 and HE4 levels show significant difference before and after chemotherapy (P <0.001). There is an established threshold range for various commercial CA125 assays, while thresholds for HE4 have been reported only recently but remain uncertain.

HE4 serum levels are related to progression of disease stage and hence to tumor burden. A failure of HE4 levels to normalize at the completion of primary therapy could be related to persistent disease neither detected by CA125 nor by physical examination or CT imaging. These patients may represent a high risk group who could potentially benefit from additional treatment or more intensive monitoring. Confirmation of this HE4 behaviour in a larger number of patients is therefore required. The suggestion that HE4 is a good indicator for the remission from the disease was reported by a follow up study by Hamed et al.[18] in which it was shown that the values of HE4 correlated with the clinical response to treatment or remission from the disease, as documented by CT imaging.

CONCLUSION

Tumor-like lesions were more common than ovarian tumors mimicking ovarian neoplasm. Surface epithelial tumors were the commonest ovarian tumors followed by Germ Cell Tumors and sex cord stromal tumors in this part of country. Serum concentration of HE4, CA125 and ROMA values were significantly elevated in women with malignant epithelial tumors than benign conditions. ROMA has maximum sensitivity and specificity compared to CA125 and HE4 values individually. In treatment response, all the parameters showed significant difference before and after treatment.

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