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Research Article

TO STUDY CLINICO-PATHOLOGICAL CORRELATION OF OVARIAN TUMORS AND TUMOR LIKE LESIONS WITH ROLE OF CA125 AND HE4 AS DIAGNOSTIC BIOMARKERS FOR DISCRIMINATION OF BENIGN AND MALIGNANT OVARIAN TUMORS IN INDIANS

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ABSTRACT

Back ground of the study: One of the greatest challenges in modern gynecological oncology is ovarian cancer. Despite the numerous studies currently being conducted, it is still sometimes detected at late clinical stages,where the prognosis is unfavorable. One significant contributing factor is the absence of sensitive and specific parameters that could aid in early diagnosis. Ovarian cancer is the deadliest gynecologic cancer, being recognized as the fifth cause of death due to cancer in women in worldwide. In more than 70% of cases, it is only diagnosed at an advanced stage. 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. Discussion and Conclusion: 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.

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INTRODUCTIO

Ovarian cancer (OC) is a gynaecologic malignancy that forms via two different carcinogenicmechanisms. These are subsequently classified into two types based on the site of origin. Type IOC tends to be comparatively more genetically stable and develop from known precursor lesions. By contrast,

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type II OC tends to be high-grade serous carcinomas which are aggressive tumours derived from fimbriae of the fallopian tube. [1] OC is commonly present late in the disease course due to its latent symptoms and insidious onset.

Around 60% of patients have International Federation of Gynaecology and Obstetrics
(FIGO) stage III–IV disease at initial diagnosis and this is associated with 5-year survival rates of 27% and 13%, respectively. Only 30–40% of patients have FIGO stage I–II at diagnosis, which is associated with a 5-year survival rate of more than 80%. Altogether, this makes it the fifth and sixth most common cause of cancer-related death in the United States and the United Kingdom,respectively, and the gynaecologic malignancy with the worst prognosis overall. [2–4]

CA125 measurement is an important component of the workup of a woman with an adnexal mass [5]. In women with tumors classified as potentially malignant with ultrasound, higher CA125 levels were associated with an increased risk of finding a histologically malignant tumor [6-8]. Unfortunately, in premenopausal woman, abnormal CA125 levels may be associated with benign conditions such as endometrioma, follicular cysts, cystadenoma, abscess, and pregnancy. High serum concentrations of CA125 are also found in women with pancreatic, stomach, colon and rectum cancers, as well as in metastatic disease [9]. This explains the tremendous amount of effort that has been spent in finding new ovarian cancer serum markers that could be used together with, or instead of, CA125 [10].

HE4 (human epididymis protein 4) is a relatively new serum marker for the diagnosis of ovarian cancer. HE4 has been shown to display increased sensitivity for detecting ovarian cancer compared to that of CA125 alone [11-12] developed a mathematical model to classify patients with a pelvic mass into high-risk or low-risk groups for having EOC, the Risk of Ovarian Malignancy Algorithm (ROMA), which combines CA125 and HE4 levels along with menopausal status in a logistic regression model. In recent studies, the ROMA index has beenshown to outperform the Risk of Malignancy Index [11]. In a meta-analysis including 11 studies from Africa, Europe and North America [13], the ROMA index has been shown to distinguish EOC from benign pelvic masses. The ROMA index was less specific but more sensitive than
HE4. However, the ROMA index and HE4 were both more specific than CA125. HE4 levels in healthy women were associated with age, and one recent study showed that the median serum HE4 levels in premenopausal women is significantly lower than in postmenopausal women [14].

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.[15]

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. [16]

Furthermore, the sensitivity and specificity of CA125 are not high enough for population screening for the detection of early stage ovarian cancer.[17] 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.[18]

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.

To study Clinicopathological correlation with histological subtypes of ovarian tumors and tumor like lesions,to find out the spectrum of ovarian tumors and tumor like lesions Sri Lakshmi Narayana Institute of Medical Sciences,Pondichery and Maharajah's Institute of Medical Sciences, Nellimarla,vizianagaram and 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.

MATERIAL AND METHODS

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 SLIMS,Pondichery and Maharajah's Institute of Medical Sciences, vizianagaram

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 3M//ml and 70 pm respectively based on the study of [19] 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.[20] 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 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%).

Table 4 and 5 shows 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 6 shows different ovarian tumors comparision in % in various studies. Among the individual tumors, Table 7 shows comparisons of serum marker n ROMA values in various studies.

Table1: Distribution of ovarian tumors and tumor like lesions (N=233)

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

Table2: Distribution of different tumor like lesions of ovary (N=137)

Tumorlikelesions	No.ofcases	%
Follicular cyst	102	74.6
Corpuslutealcyst	27	20
Endometriosis	04	2.7
Inclusion cyst	04	2.7
Total	137	100

Table3: 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

Table4: Serum CA125, HE4 and ROMA values in ovarian tumors (N=96)

Tumor	CA125median (u/ml)	HE4median (pmol/l)	ROMA (%)
Benign			
Cystadenoma / Cystadenofibroma	12.6	53	8.4
Fibroma /thecoma	30	48	7.1
Matureteratoma	24	47	6.7
Malignant			
Epithelial ovarian carcinoma	558	238	80.5
Metastatic tumors	785	184	80.6

Table5: Level of HE4 and CA125 in ovarian cancer group before and after treatment (N=96)

	Before treatment Median (range)	After treatment Median(range)	Pvalues
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

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

Ovarian tumors	Pilli etal	Bodal V K etal	Kanthikaretal	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	Terlikowaskaetal[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%

DISCUSSION

Modern research techniques based, among other things, on molecular biology allow a continuous expansion of research aimed at finding more and more effective biomarkers for ovarian cancer. There is a search for a complementary parameter to the most commonly used CA125 or HE4, which would satisfactorily increase the sensitivity and specificity of the determinations. Among potential biomarkers, microRNAs, autoantibodies, cDNAs,

The CA125 antigen is one of the most extensively researched markers employed in ovarian cancer diagnosis. However, its use in clinical practice faces controversies resulting from the sensitivity and specificity of the test [19]. While its applicability in earlystage screening for ovarian cancer is uncertain, it is utilized as an indicator to appraise chemotherapy effectiveness and assess prognosis [20-21]. Gupta D et al. [21], after reviewing the epidemiological literature, concluded that serum CA125 levels in serum are a powerful predictor of overall and progression-free survival in patients with OC. The researchers' analysis of the data showed that decreasing levels of CA125 indicate a positive response to cancer therapy, while rising levels indicate a relapse of the cancer [21].

Adipocytokines, and galectins are drawing the attention of researchers. CA125 is a commonly used marker in the diagnosis of ovarian cancer. However, it lacks the specificity and sensitivity required for reliable early detection of the disease, as only 50% of early-stage ovarian cancer cases have elevated CA125 levels. Additionally, elevated CA125 levels can be associated with many other conditions [22]. Other markers,such as HE4, or algorithms, such as ROMA, are also used for diagnosis. However, the search for a marker or combination of markers that meets the criteria of an ideal

marker is ongoing. When comparing the sensitivity/specificity of a single CA125 test and the sensitivity/specificity of combinations of CA125 with other markers, we see that in most cases combinations perform better than a single test. It is very difficult to select parameters that meet the criteria of an ideal screening test (SN 75%, SP 99.6%). Among the combinations analyzed in this article, two sets meet these requirements: CA125 + HE4 + Segfr (SN 83.3%, SP 100%) and CA-125 + HE4 + E-CAD + IL-6 (SN 86.4%, SP 100%).

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. (23-24) This study accounted for 50.1% cases of serous cystadenoma which is comparable to studies by Misra et al Pilli etal and Maheshwari et al who reported incidence of serous cystadenoma, that is, 49% and 46.01%, respectively. (25-26,23) Mucinous cystadenoma accounted for 7.3% cases of neoplastic lesions. Higher incidence have been reported (13%).14,11 3.0% cases of mucinous cystdenocarcinoma were reported in present study, while showed an incidence of 0.25%, 4%, and 5% respectively. [23,27] There were 3.2% cases of granulosa cell tumor and it was slightly more compared to the study done [28] Mature cystic teratoma, most common germ cell tumour, accounted 18.7% of total neoplastic lesions. Studies which showed an incidence of 18.46%, 23.13% and 15.45% respectively [29,24,30]

Our results shown 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. [31] 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

In summary, OC is a highly lethal disease, owing to its insidious onset and late detection. Currently, CA125 and HE4 are the only approved biomarkers for use in EOC; however, they are not sufficient for early detection, thus novel diagnostic biomarkers are a necessity. Multiple biomarkers across various platforms have been identified that may have potential as a diagnostic or screening tool in the early detection of OC. Further research is required to better understand these biomarkers and improve their diagnostic accuracy in OC which could help accelerate their translation to clinical practice.

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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