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A Study on Correlation of Tumor Markers and Histopathology in Ovarian Mass

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Abstract

Background: Most ovarian cancers are detected in the late stages as there are nearly no clinical symptoms or signs at the early stage. Its high mortality rate has made it one of the most investigated fields in gynecological oncology.

Aim: To study correlation between serum tumor markers and histopathology in diagnosed and operated cases of ovarian mass.

Objectives: To study tumor marker levels in diagnosed and operated cases of ovarian mass and post operatively with the histopathology of said specimen.

Settings and design: This is a prospective observational study carried out in a tertiary health care centre over 2 years from October 2019 to October 2021.

Materials and Methods: The study population included 50 women diagnosed with an ovarian mass and operated for the same.

After obtaining consent from the patient, detailed history was obtained, physical examination was done to examine the mass. Serum analysis for levels of tumor markers such as CA-125, b-HCG and Serum Lactate Dehydrogenase were assessed. Patient was investigated using ultrasound and if required MRI studies was also done.

Post operatively, specimens were sent for histopathological studies.

Conclusion: Among the tumor markers researched in this study, serum LDH can detect and predict the histological pattern of ovarian cancers as well as the malignant potential of the tumors. However, CA125 is able to predict only the malignant potential of the tumor. Beta hCG has no role in predicting the histology or malignant potential of tumors.

Keywords: Tumor markers, Ovarian mass.

Introduction

Among all gynecological malignancies, ovarian cancer is the most difficult in diagnosis as well as treatment. Ovarian cancer is the most common cause of death from gynaecological cancers. In India, after cervix and breast cancer, ovarian cancers are ranked the third most common malignancy.[1] The ovary has a complex histology owing to the constant cyclical change from puberty to menopause. During normal ovulatory cycles, ovary undergoes traumatic insults and endocrine changes making it susceptible to carcinogenesis. Although no age group is free from tumors, different tumors tend to involve different age groups preferentially.

Most ovarian cancers are detected in the late stages as there are nearly no clinical symptoms or signs at the early stage. Studies have shown that only <25% of patients with ovarian cancer can be diagnosed at the early stage and 70% of patients are diagnosed at the advanced stage. In early-stage ovarian cancer, the 5 years survival rate is 80-90% if effective treatment is available.

Malignant tumors have usually spread outside the ovary by the time a definitive diagnosis is made. Abdominal pain and distention, urinary and gastrointestinal tract symptoms due to compression by the tumor or cancer invasion are the most common symptoms. The benign forms may be entirely asymptomatic and occasionally are found unexpectedly on abdominal or pelvic examination or during surgery. This type of gynecological malignancy is either diagnosed by chance (e.g., during a diagnostic laparoscopy) owing to the fact that in early stages it is almost symptomless, or when it is already in an advanced stage that gives rise to symptoms.

Relatively poor 5 and 10 years survival rates for these patients, compared with rates in cervical and endometrial carcinoma. For these reasons, both early diagnosis and prevention are top priorities.

Its high mortality rate has made it one of the most investigated fields in gynecological oncology.

CA 125 is the most reliable serum marker for ovarian carcinoma. Normal CA 125 levels are less than 35 U/ml. It has a significant role in monitoring treatment and detecting recurrence of ovarian cancer. It has prognostic value in advanced ovarian cancers. CA 125 is expressed by over 80 % of ovarian cancers and levels at present correlate with the risk of malignancy, stage of disease and histology.[2] In addition, we have other tumor markers significant in relation with ovarian tumors, like beta-HCG and serum LDH levels.

LDH is known to be a non specific cancer diagnostic parameter. Elevated beta HCG was found to be of poor prognostic value and indicator of resistance to therapy in cancer patients.[3]

HCG includes a group of five molecules with a common amino acid sequence only differing in multimeric structure and carbohydrate side chain structure. Out of these 5 molecules, beta HCG and hyperglycosylated beta HCG were confirmed to be associated with advanced stage carcinomas4. In this study we will be correlating the 3 tumor markers i.e., CA 125, beta-HCG and serum LDH in relation to its pre-operative value and the histopathology in diagnosed and operated cases of ovarian tumors.

Materials and Method

A prospective observational study was carried out in 50 women diagnosed with ovarian mass and operated for the same between October 2019-October 2021. The purpose and the procedure of the study was explained to them and a written consent was obtained.

Inclusion Criteria

All the operated cases of ovarian mass diagnosed clinically and confirmed by sonography and if required MRI, irrespective of their clinical features, stage of the disease or type of surgical procedure implemented were included.

Exclusion Criteria

1. Pregnant patients with ovarian mass
2. Cases of Abdominal and genital TB

Statistical Analysis

The data was recorded into a spreadsheet in Microsoft excel. Qualitative data was expressed in form of percentages while quantitative data were expressed as mean ±SD and range values. The relationship between qualitative data were tested using Chi-square or Fisher's exact test and for quantitative data independent sample't' test was used. Lastly, univariate and bivariate analysis were to done to calculate odds ratio with confidence interval and p-value that depicted the strength of association. For analysis, $p < 0.05$ was considered statistically significant. The data were subjected to statistical analysis using the SPSS (Statistical Package for the Social Sciences) version 24.0 software.

Results

The mean value of CA125 in 50 women was 62.45 ± 267.45 with minimum value of 4.00 and maximum value of 1912.00.

While the mean value of LDH in 50 women was 425.44 ± 160.55 with minimum value of 196.00 and maximum value of 1104.00

In the present study, among the ovarian tumor in 50 women, beta- hCG was less than 1.20 in 78% and it was more than equal to 1.2 in 22%.

Table 1: Descriptive statistics of tumor markers

Tumor markers	N	Mean ± S.D	Minimum value	Maximum value
CA-125 (U/ml)	50	62.45 ± 267.45	4.00	1912.00
LDH	50	425.44 ± 160.55	196.00	1104.00

Table 2: Distribution of study subjects according to histological subtypes

Histology	Frequency	Percentage
Functional cysts	5	10.0
Surface epithelium	40	80.0
Germ Cell tumors	3	6.0
Sex cord stromal	2	4.0
Total	50	100.0

On histological examination in the present study among 50 women; 10% of the ovarian tumors were functional cysts, 80% were surface epithelium tumors, 6% were of germ cell origin and 4% were sex cord stromal tumors.

On assessing the nature of tumor in the present study among 50 women; 92% of all the ovarian tumors were benign, 6% were malignant and 2% were borderline.

Table 3: Correlation between histology and serum CA 125

Histology	CA-125	ANOVA
Functional cysts	27.70 ± 9.67	
Surface epithelium	69.74 ± 29.24	F= 0.080 p=0.923
Germ Cell	50.27 10.75±	
Sex cord stromal	55.60 ± 14.70	

The mean CA-125 value among functional cyst was 27.70 ± 9.67, surface epithelial cell, tumors was 69.74 ± 29.24 and sex cord stromal tumors were 55.60 ± 14.70. The difference in mean among the histological variants was not statistically significant (F=0.080, p=0.923) stating that CA-125 as a tumor marker will not be able to differentiate among histological subtypes.

The mean LDH value among functional cyst was 393.13 ± 107.77, surface epithelial cell tumors was 416.03 ± 134.70 and sex cord stromal tumors was 743.00 ± 510.53.The difference in mean among the histological variants was statistically significant (F=4.782, p=0.013) stating that LDH as a tumor marker will differentiate among histological subtypes.

The mean CA-125 value among benign tumors was 23.48 ± 16.71, borderline tumors was 34.00 ± 0.0 and malignant tumors was 669.50 ± 1076.18. The difference in mean among the tumors based on malignant potential was statistically significant (F= 11.86, p=0.001) stating that CA-125 as a tumor marker will differentiate among the tumors based on the malignant potential.

The mean LDH value among benign tumors was 401.17 ± 100.61, borderline tumors was 385.00 ± 0.0 and malignant tumors was 811.00 ± 408.00. The difference in mean among the tumors of based on malignant potential was statistically significant (F= 14.14, p=0.001) stating that LDH as a tumor marker will differentiate among the tumors based on the malignant potential.

While asssessing the association between histology of ovarian tumors and beta Hcg levels, 66% of the women had beta hCG<1.2 and 34% had hCG levels ≥1.2. Amongthe tumors with beta hCG<1.2, 93.3% were surface epithelium tumors and 6.1% had functional cyst. While among tumors with hCG levels ≥1.2, 52.9% were surfaceepithelium, 35.3% were functional cysts and 11.8% were sex cord stromal tumors.

There was no statistically significant association between the histology and beta- hCG ($\chi 2$=0.24, p=0.565) stating that as tumor markers hCG will not be able to predict the histology of the ovarian tumors.

While assessing the association between malignant potential of ovarian tumors and beta hCG levels, 78% of the women had beta hCG<1.2 and 22% had hCG levels ≥1.2.

Among the tumors with beta hCG<1.2, 92% were benign tumors, 3% borderline tumors and 5% were malignant tumors. While among tumors with hCG levels ≥1.2, 91% werebenign tumors and 9% were malignant tumors. There was no statistically significantassociation between the malignant potential and beta-hCG ($\chi 2$= 0.508, p=0.77) statingthat as tumor markers hCG will not be able to predict the malignant potential of theovarian tumors.

Discussion

CA125 and ovarian cancer.

In the study by Kadayifci A et al., stated that serum CA125 levels in patients of ovarian cancers was elevated >35U/ml in 87%. The mean CA125 levels were 825.9 ± 188U/ml. Similarly in the study by Stephen C et al., All patients had documentation ofan elevated CA 125 level (>35 U/ml) at a time when ovarian cancer was present. In the present study all the study participants had an ovarian tumor and amean CA125 of 62.45 ± 267.45 was observed with minimum value of 4 and maximum value of 1912.

Association of CA125 with histology of ovarian tumor.

In the present study no association was observed between CA125 levels and histology of ovarian tumors. Kolwijcket al. describe that the pre-operative serum CA 125 levels are significantly higher in advanced lesions and in serous tumors. Rosai describes that the histology and the disease stage are associated with serum CA 125 levels. This discrepancy in results could be due to regional and ethnicity variation.

Association of CA125 with malignant potential of ovarian tumor.

In the present study a statistically significant association was observed between malignant potential of ovarian and CA125 levels and the mean value of CA125 in benign, borderline and malignant tumor was 23.48 ± 16.71, 34.00 ± 0.0 and 669.50 ± 1076.18 respectively. It meant that CA125 was able to identify the malignant potential and the mean for malignant ovarian cancers was significantly higher than the benign cancers. Similar association was observed in the study by Cambruzzi et al., where serum CA 125 levels ranged from 5 U/ml to 408 U/ml and serum CA 125 level wasassociated with the biological behavior of the neoplasm (malignant or benign - p =0.002). in another study by Prakash et al., there was statistical significant associationbetween malignant potential and mean serum as the mean value of serum CA-125 was47.09 ± 93.68(IU/ml among benign cases, 101.37±131.58(IU/ml in borderline casesand 572.45±368.48 (IU/m among malignant cases.

Association of LDH with histology of ovarian tumor.

On analysis, Konishi I et al. observed that LDH is a useful marker for identification of germ cell tumors. Similar results were observed in the present study as a significant difference was observed among different histological types of ovarian cancers. The mean levels of LDH was maximum for germ cell tumors (743.00 ± 510.53) and minimum for functional cyst (393.13 ± 107.77).

Association of LDH with malignant potential of ovarian tumor.

Mixed reports are available regarding the activity of LDH in ovarian tumors. In the study of Bagde N et al., no difference in LDH was observed among malignant vs benign ovarian cases. High LDH levels have been associated with ovarian and extragonadaldysgerminomas however older studies did not report a significant association between LDH and ovarian tumors. Another study supporting the association of LDH levels and malignant potential was by Xiang J et al serum LDH levels in malignant ovarian tumors were significantly higher as compared to those those with benign ovarian tumors.

Similarly, Simaga S et al. found a significant rise

in LDH-specific activity in malignant tumors of the ovary, but not in benign neoplasms, compared to the activity in normal tissue.

According to the present study, a significant difference was observed in mean LDH levels of benign, borderline and malignant ovarian tumors with the mean being highest for malignant tumors (811.00 ± 408.00). Hence, serum LDH can be used a tumor marker to identify the malignant ovarian tumors cancers.

Association of beta-HCG with histology of ovarian tumor.

In the present study, no significant association was observed between beta HCG and histology of ovarian tumors. Lenhard M et al stated that though a statistically significant difference was observed in HCG expression related to tumor grade but no such difference was observed with regards to the histology subtype.

Similary, other study by Djurdevic et al. depicts no significant difference between β-hCG levels and different histological groups of tumors were observed.

Association of beta-HCG with malignant potential of ovarian tumor.

JL Vaitukaitis stated that patients with tumors of the ovary were found to have highest incidence of ectopic hCG secretion suggesting it to be a good marker to identify ovarian cancers. A study by Zygmunt states that in vivo, hCG induced neovascularization comparable to the activity of vascular endothelial growth factor. HCG-secreting tumors indicate the importance of HCG in tumor growth. However, the results observed in this study state that there is no statistically significant difference between HCG among benign and malignant cases indicating that HCG is unable to identify the malignant potential in ovarian cancers.

Conclusion

Among the tumor markers evaluated and researched in this study, serum LDH can detect and predict the histological pattern of ovarian cancers as well as the malignant potential of any tumors. However, CA125 is able to predict only the malignant potential of the tumor. Beta-hCG has no role in predicting the histology or malignant potential of tumors as such.

Further study needs to be conducted for assessing the accuracy of these tumor markers (LDH, beta-hCG and CA125). Also, predictive value of the tests should be calculate when these tumors markers are used in combination. These tumor markers may provide insights towards early detection of the malignancy.

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