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Study of Changes in Biochemical Parameter Ca-125 in Ovarian Tumors before and after Chemotherapy

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Abstract: ***Introduction: The cancer burden in India is given in Gynaecological cancers occur in about 6.8% population. The lifetime risk of developing sporadic epithelial ovarian cancer is approximately 1.7% although patients with a familial predisposition have a much higher lifetime risk in the range of 10 to 40%. Serum CA125 is the only serum marker available with potential accuracy to be beneficial. But even this marker is less than optimal. Approximately 50% of patients with early-stage ovarian and other cancers do not have elevated serum CA125 levels. Also, a variety of nonmalignant and non ovarian malignant conditions can result in elevated serum CA125 levels. The current study designed with an aim to explore the changes in CA125 in malignant and benign ovarian tumours pre therapy and post therapy. To explore the differences in CA125 between healthy individuals and patients with ovarian tumors. Methodology: A case study control was conducted on 40 patients suffering from ovarian tumors (Benign and Malignant) who had reported to Rangaraya Medical College and hospital, Kakinada after ethical committee clearance and informed the consent from the patients. Results: All statistical analysis was done using SPSS software and results were obtained The mean age of the patients were found to be 44.77 ± 11.66. Mean age of the patients with malignant tumors (n=29) was 47.7 to ± 9.26 years whereas for benign tumors (n=11) it was only 37± 4.34 years. All patients with ovarian tumours (both malignant & benign) had a pretreatment mean ± SD value of CA125 of 767 ±1069 U/ml which reduced to a mean± SD value of 46.28 ± 41.28 U/ml post treatment (p< 0.0004). Conclusion: The changes in CA125 levels were significant in both malignant and benign tumors thus reinforcing the importance of its role as a biomarker in ovarian neoplasm especially in epithelial ovarian cancers.***

Keywords: Ovarian neoplasm, CA 125, epithelial ovarian cancers

1. Introduction

Ovarian cancer is the malignant proliferation of ovarian cells arising from the ovary. It represents a spectrum of disease entities which arise from various cells such as epithelial, germ cell or sex cord stromal cells. Epithelial ovarian cancer arises from epithelial cells and typically occurs in postmenopausal women. In contrast, most germ cell tumours present at a younger age while sex cord stromal tumours may occur at any age. Approximately 90% of ovarian tumours are epithelial in origin. Managing these cancers poses significant therapeutic challenges as they present at an advance stage and tend to recur in majority of the cases. In contrast other malignant ovarian tumours like germ cell and sex cord stromal tumours are often localized in distribution, and amenable to complete surgical resection thus having a favorable prognosis[1].

Although majority of the ovarian cancers arise from the surface epithelium of the ovaries. However, a minority of these tumours also arise from the epithelial lining of the fallopian tube. Since ovaries and tubes are closely related to each other, it is thought that these fallopian cancer cells can mimic ovarian cancer.

The cancer burden in India is given in Gynaecological cancers occur in about 6.8% population.. The lifetime risk of developing sporadic epithelial ovarian cancer is approximately 1.7% although patients with a familial predisposition have a much higher lifetime risk in the range of 10 to 40%[2]. The median age at diagnosis for sporadic disease is 60 years although patients with a genetic predisposition may develop this tumour earlier, often in their fifth decade.

Early ovarian cancer is diagnosed by surgical evaluation of an adnexal mass[3]. The decision to subject a patient to surgical exploration is difficult to make, however. Ultrasonography evaluation of adnexal masses has not improved only the ability to distinguish patients who should have surgical exploration from patients who can be further evaluated through observation, but it also has resulted in an increasing number of patients who are found to have an asymptomatic ovarian cyst. This result is of particular concern in postmenopausal women.

The use of tumor markers to assist in evaluation of a patient with an adnexal mass is appropriate, but misinformation may result. Serum CA125 is the only serum marker available with the potential accuracy to be beneficial, but even this marker is less than optimal[45]. Approximately 50% of patients with early-stage ovarian and other cancers do not have elevated serum CA125 levels. Also, a variety of nonmalignant and non ovarian malignant conditions can result in elevated serum CA125 levels.

CA-125 is a high molecular mass (greater than 200KDa) glycoprotein recognized by the monoclonal OC 125[6] .It contains 24% carbohydrate and is expressed by epitheloid ovarian tumours and other pathological and normal tissues of mullerian duct origin.

In healthy population the upper limit of CA 125 level is 35 units/ml. CA 125 is elevated in non-ovarian carcinoma ,

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including endometrial , pancreatic, lung , breast and colorectal and other gastro intestinal tumors. It is also elevated in women in the follicular phase of the menstrual cycle and in benign conditions like cirrhosis, hepatitis, endometriosis pericarditis, and early pregnancy. CA 125 is not useful in screening for ovarian cancer in asymptomatic population .It cannot be used to differentiate ovarian cancer from other malignancies[7].

In ovarian cancer, CA 125 is elevated in 50% of patients with stage-I disease, 90% with stage-II and more than 90% with stage-III & IV .The level of CA 125 corresponds with tumor size and staging, CA 125 is also useful in differentiating benign from malignant disease in patients with palpable ovarian masses[8]. This differentiation is important because surgical intervention for malignant ovarian masses is far more extensive than that for the begin masses. Einhorn and colleagues studied 100 patients undergoing diagnostic laparatomy for palpable adnexal masses; of these 23 were found to have a malignancy. Using 35U/ml as the cut off value, the predictive value for malignant disease were 78% sensitivity, 95% specificity, 82% positive predictive value and 91% negative predictive value. Tumor differentiation does not affect the CA 125 level.

A pre operative CA 125 level[9] of less than 65U/ml is associated with a significantly greater 5 year survival rate (42%) than is a level greater than 65U/ml (5%). Postoperative CA125 levels and the rate of decline are also predictors of survival. The half life of CA 125 is normally 4.8 days. A group of patients with a CA125 half life of 22 days responded poorly to chemotherapy as compared with another group with a CA125 half life of 9 days.

CA 125 is useful in detecting residual disease in cancer patients following initial therapy. The sensitivity of CA 125 for detecting tumour, before repeat laparotomy is 50% and the specificity is 96%. After chemotherapy, the CA 125 level provides an indication of disease prognosIs. A decrease in the CA 125 level by a factor of 10 after the 1st cycle of chemotherapy is indicative of improvement. Persistent elevation of CA-125 levels after 3 cycles of chemotherapy indicates a poor prognosis[9].

In the detection of recurrent metastases, use of CA-125 level as an indicator is about 75% accurate. The lead time from CA-125 elevation to clinically detectable recurrence is about 3 to 4 months. CA-125 correlates with disease progression or regression in 80% to 90% of cases.

2. Review of Literature

Markman in her paper has shown the effectiveness of CA125 in not only screening of ovarian cancer but also in evaluating the efficacy of anti-neoplastic agents. Her study showed a 50% decrease in the levels of CA125 after 2 samples or a 75% decrease over 3 samples can be considered acceptable for responding patients. Furthermore, a larger percentage decrease and a more rapid fall in the antigen levels indicate greater tumour cell kill. A rising levels during or after therapy is an indication of failure of therapy and presence of residual disease. She concluded that the rate of rise or fall in CA125 levels can be used as a surrogate marker for effectiveness of anti-neoplastic method[11].

A retrospective analysis was performed on 300 patients with EOC with at least one measurement of CA-125. The date of progression according to clinical or radiologic criteria was ascertained in 88 patients with persistently elevated CA-125 levels (>23U/ml).This was compared with date of progression according to CA-125, defined as the date on which CA-125 level first increased to ≥ twice its nadir level confirmed by a second sample also ≥ twice the nadir.80 of the 88 patients had evidence of progression by the standard and CA-125 criteria giving sensitivity of 94%.In 13 patients CA-125 doubly occurred after the date of clinical progression[12]. Only one patient had a pulse positive prediction of progression according to CA-125. The patient died as a result of MI before evidence of clinical progression. In patients whose CA-125 level decreases to normal after chemo therapy[11,12,13,], a doubling from the upper limit of normal has been shown to predict progression. In those with persistently elevated levels, doubling of CA-125 from its nadir level has accurately defined progression. If confirmed the CA-125 criteria should be used as additional end points in clinical trials.

Zurawski V.R et al analyzed serum samples for CA-125 levels and suggested that, if CA 125 used in conjunction with other tests could discriminate ovarian Carcinoma from other disorders that could elevate CA-125 levels.

Einhorn N, et al showed that specificity of CA-125 level is adequate in post menopausal women to undertake a larger study to determine whether screening using CA-125 influences survival of patients with ovarian cancer.

Kucukgoz U et al conducted Comparative analysis of CA-125, Ferritin, Beta 2 Micro Globulin, and LDH levels in serum and peritoneal fluids in patients with ovarian neoplasm. The Study concluded that CA-125 is the most important bio marker for Epithelial Ovarian cancers. Beta-2 Micro Globulin is a new marker for epithelial ovarian cancers. However further studies are required for this marker.

Robyn Anderson et al Combined symptoms index with CA-125 to improve detection of ovarian cancer. This combination of CA-125 and symptom index identified more than 80% of women with early stage disease with greater sensitivity than CA-125 alone[13].

It is known that panel of 4 serum biomarkers effectively detected early-stage ovarian cancers with the highest reported overall sensitivity of 96%. Endometrioid tumors were detected at early stages with a sensitivity of 98%.

Prospective clinical analysis of the panel is needed to validate it as an effective screening tool for early-stage ovarian cancer

Aims and Objectives

- To explore the changes in CA125 of malignant and benign ovarian tumours pre therapy and post therapy.

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- To explore the differences in CA125 between healthy individuals and patients with ovarian tumors.

3. Materials and Methods

Study type: case control study
Place of study: Rangaraya Medical College & General Hospital, Kakinada
Study Period: March 2019 to January 2020

Selection criteria:

Exclusion criteria:
1) Patients diagnosed with other malignant tumors
2) Patients older than 65 years

Inclusion criteria: patients diagnosed with ovarian tumors

4. Procedures

CA-125– CLIA Method using IMMUNOCHEMISTRY FULLYAUTOMATED ANALYSER

The present study was conducted in the Department of Biochemistry, Rangaraya Medical College, Kakinada, Andhra Pradesh. The present study was undertaken to study the serum of patients with ovarian tumors before and after therapy (Surgery and/or chemotherapy) after ethical committee clearance and informed concent from the patients The serum of 40 patients of ovarian tumors was taken out of which 11 were benign tumors and 29 were malignant tumours. The values were compared with the values of 40 healthy women taken as Control groups. All the subjects were accrued from the department of Gynaecology, Govt. General Hospital who were admitted for treatment. Demographic and clinical data were collected at routine Gynaecology visits. Blood samples were obtained by venous puncture from the antecubital vein of each woman before and after therapy (Surgery and/or Chemotherapy). The control group denied any history of chronic disease and of same age group and test group. Consent was obtained from both the cases and control groups. Serum was separated and analyzed by using standard methods. The observed values were compared with control group for statistical analysis. All data were expressed as Mean ± Standard deviation and standard error of mean. Differences with a P-value of less than 0.05 were considered to be stastically significant.

5. Observation and Results

The study was approved by the institutional scientific and review committee. We present our observations on the demographic, treatment and biochemical profile ovarian tumours (benign and malignant) pretreatment and post treatment and compared them with matched healthy individuals. We accrued 40 healthy female individuals and 40 patients with ovarian tumours of which 29 patients had malignant ovarian cancers (epithelial and non epithelial) and 11 patients had benign ovarian cysts) over a period of 1.5 years.

Table 1: Demographic profile of Patients with Tumours and treatment parameters

Patient and tumour profile		*Frequency*	*%*
Age (N =40)	Mean age :44.77 years Median Age: 48 years Mean ± SD: 44.77± 11.76 Mean± SEM:44.77 ± 1.86		
	Range:13- 65yrs		
Duration of symptoms For all patients (N =40)	Mean duration 12. 6 weeks Median duration: 6.5 weeks Mean ± SD:12.61± 20.89 Mean± SEM: 12.61± 3.30		
	Range :0.4 -104 weeks		
Duration of symptoms for patients with malignant tumours (N = 29)	Mean duration: 8.62 weeks Median Duration: 6 weeks Mean ± SD:8.62 ± 12.50 Mean± SEM:8.62 ± 2.32		
	Range: 0.6 -52 weeks		
Duration of symptoms for patients with benign tumours (N = 11)	Mean Duration: 23.1 weeks Median duration: 8 weeks Mean ± SD:23.1 ± 33.1 weeks Mean ± SEM:23.1 ± 9.98 weeks		
	Range: 0.4 - 104 weeks		
Histology of tumour (N =40	Benign Cyst Serous Cystadenocarcinoma Mucinous Cystadenocarcinoma Granulosa cell tumour Yolk sac tumour Cyst adenoma	10 12 15 1 1 1	25 30 37.5 2.5 2.5 2.5
Type of tumour (N = 40)	Benign	11	27.5
	Malignant	29	72.5
Age of pts with malignant tumours (N = 29)	Mean Age: 47.72 years Median Age: 49 years Mean ± SD: 47.72 ± 9.26 years Mean± SEM:47.72 ± 1.72 years		

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	Range:15- 65 years		
Age of pts with Benign Tumours (N = 11)	Mean Age: 37 years Median Age: 40 years Mean ± SD: 37 ± 14.4 years Mean ± SEM : 37 ± 4.34 years		
	Range: 13—56 years		
Medical history (N = 40)	Hypertension Diabetes Anemia Hypertension with hypothyroidism No Medical history History Not available	3 1 1 2 29 4	7.5 2.5 2.5 5.0 72.5 10.0
Treatment profile		**Frequency**	**%**
No of Chemotherapy cycles in patients with malignant tumours (N = 29)	Mean : 5.4 cycles Median: 6 cycles Mean ± SD: 5.4 ± 1.27 cycles Mean± SEM:5.4 ± 0..23 cycles Range: 1 – 6 cycles		
No of chemotherapy cycles (N = 29)	Pts who had 6 cycles Pts who had 5 cycles Pts who had 3 cycle Pts who had 1 cycle	23 2 3 1	79.3 6.9 10.3 3.5
Surgery	Complete Incomplete No surgery	35 3 2	87.5 7.5 5.0
Patients with Malignant tumours (N = 29)	Chemotherapy only Neoadjuvant chemotherapy +Surgery Surgery +Adjuvant Chemotherapy	2 1 26	6.9 3.5 89.6

Table 2: Profile of healthy female individuals (N = 40)

Parameters	Mean	Median	Mean ± SEM	Mean ± SD	Range
Age (years)	44.02	44	44.02±1.47	44.02±9.36	27-70
CA125 (U/Ml)	15.48	17.25	15.48±0.71	15.48±4.49	5.70-22.30

Table 3: Biochemical profile of patients for all Ovarian Tumours (pre-treatment and Post treatment) [N= 40]

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range
CA125 (U/Ml)	Pre	767	563.3	169.1	1069	3.4- 4784
	Post	46.28	25.75	11.35	71.81	2.9-350

Table 4: Changes in Pretreatment and post treatment biochemical parameters in benign ovarian tumours

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range	P- Value
CA125 (U/Ml)	Pre	97.93	35	39.23	130.1	3.4-361	0.002
	Post	18.35	18	2.82	9.37	2.9-35	

Table 5: Changes in Pretreatment and post treatment biochemical parameters in malignant ovarian tumours

Parameters	Pretreatment/Post treatment	Mean	Median	± SEM	± SD	Range	P- Value
CA125 (U/Ml)	Pre	940.3	594.5	222.8	1200	14-4784	0.0005
	Post	57.64	34.00	15.17	81.67	10-350	

Table 6: Changes in Pretreatment and post treatment biochemical parameters in ovarian tumours (benign & Malignant)

Parameters	Pretreatment/Post treatment	Mean	Median	± SEM	± SD	Range	P- Value
CA125 (U/Ml)	Pre	767	563.3	169.1	1069	3.4-4784	**0.0004**
	Post	46.28	25.75	11.35	71.81	2.9-350	

Table 7: Biochemical profile of healthy female individuals (controls) vs. females with ovarian tumours. (N = 40)

Parameters	Controls/ Tumours	Mean	Median	± SEM	± SD	Range	P-Value
CA125 (U/Ml)	Controls	15.48	17.25	0.71	4.49	5.70-22.30	0.0001
	Ovarian tumours	767.00	563.3	169.1	1069	3.4-4783.50	

6. Discussion

A study was conducted on 40 patients suffering from ovarian tumors (Benign and Malignant) who had reported to Rangaraya Medical College hospital, Kakinada. The demographic and treatment profile of patients with ovarian tumours are illustrated in tables 6 &7. The mean age of the patients were found to be 44.77 ± 11.66. Mean age of the

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patients with malignant tumors (n=29) was 47.7 to ± 9.26 years whereas for benign tumors (n=11) it was only 37± 4.34 years. A similar finding of mean age of 49.9 ± 17.5 years was found in a study conducted in ovarian cancer patients by Umran Kucukgoz Gulec, et al.

The mean duration of symptoms was 12.6 ± 20.89 weeks (range 0.4- 104 weeks) and the median was 6.5 weeks in our cohort of patients. The mean duration of symptoms for benign (n=11) tumors was 23.1 ± 33.1 weeks whereas for malignant (n=29) tumors the duration of symptoms was 8.62 ± 12.50 weeks. As expected the symptomatology in malignant tumours was more aggressive than benign tumours.

Majority of the patients (72.5%) had no important relevant medical history. Only 7.5% had HTN. A combination of hypertension and hypothyroidism was present in 5% of our patients, while for 10% history was not available. The presence of hypertension could be age related and may not have any bearing with disease perse as most of the patients in this study were in the 5th decade of life. Studies have shown hyperglycaemia and diabetes to be a poor prognosticator in ovarian tumours (50) although only one patient (2.5%) in this study showed overt signs and symptoms of diabetes. This study showed that a hyperglycemic patient with a glucose level of 140 mg/dL at the time of pre-surgical consultation was twice as likely to die of disease during the observation period in comparison to a patient at the bottom of the normal range (70 mg/dL). For a patient who achieved remission, a glucose level of 140 mg/dL before surgery meant being more than two times as likely to recur in comparison to a patient at 70 mg/dL resulting in lower overall survival (OS) and disease free interval (DFI).

Platinum based chemotherapy using cisplatin or carboplatin in combination with paclitaxel is the standard adjuvant therapy in ovarian cancers. In our study, the number of chemotherapy cycles in patients with malignant ovarian tumours was 5.4 ± 1.27 cycles with a compliance rate of 79.3%. (Table-6) In a study of 218 ovarian cancer patients reported from india, the compliance to chemotherapy was extremely poor at 45%. [(79)].In our study, 87.5% had complete surgery for their condition. 89.6% of patients required surgery + adjuvant chemotherapy and 6.9% took only chemotherapy as a palliative treatment due to advance stage of the disease.

The main objective of the study was to explore the changes in the CA125 levels in pre and post therapy in both benign and malignant ovarian tumours.

Recent epidemiological studies have suggested a role for hyperglycemia in the pathogenesis of a number of cancers. Significant associations have been reported between elevated glucose. glycemic load and a number of cancers, but there is little information to support the influence of preexisting hyperglycemia on Epithelial Ovarian Cancers (EOC). Although population-based studies have not been supportive for a role of preexisting hyperglycemia in the development of ovarian cancer, recent basic science still suggests that EOC may be subject to the influence of high blood sugar. The rate of glucose uptake, which increases with increasing extracellular glucose has been linked with tumor aggressiveness EOC cells are also sensitive to complete glucose deprivation than non transformed ovarian epithelial cells thus, they may also be very responsive to hyperglycemia.

In ovarian tumors CA-125 are relavent tumour markers for not only diagnosis but also for assessing response to treatment but also for prognostification of the disease as they reflect the disease burden and the disease status pre and post therapy.[(91,92)]

In our study, all patients with ovarian tumours (both malignant & benign) had a pretreatment mean ± SD value of CA125 was 767 ±1069 U/ml which reduced to a mean± SD value of 46.28 ± 41.28 U/ml post treatment ($p< 0.0004$). On comparing the CA-125 levels in benign vs. malignant ovarian tumours, as expected these markers were highly elevated in the pretreatment serum samples of malignant ovarian tumours except in germ cell and sex chord ovarian cancers. The mean CA-125 levels in benign ovarian tumours were (mean CA-125: 97.93; range: 3.4-361) while in malignant ovarian cancers (mean CA-125:940.3; range: 14-4784). In benign ovarian tumour patients the CA-125 levels were 2-3 times above the normal. However, in ovarian cancers both CA-125 was grossly elevated. Thus CA-125 can be considered as biomarker for diagnosis and prognostification of ovarian cancers as both the serum levels of both these marker reduced significantly following surgery and adjuvant chemotherapy in epithelial ovarian cancers. However, the same cannot be said in case of benign tumours as these markers did not show any significant changes pre and post treatment. The pre treatment and post treatment serum levels of CA125 summarized in tables. The reduction in the serum CA125 indicates post therapy (surgery and /or chemotherapy) indicates reduction in tumour burden which is an indirect reflection of response to therapy. We are unable to comment on the duration of response and survival of patients as the data was not collected for these patients since it would entail both clinical and biochemical follow-up at each and every visit. The findings in our study can be well corroborated with multiple other studies which have shown that serum CA-125 can be used as a prognostic marker with high accuracy (low false positive and negative). Hence all the clinical trials incorporating newer strategies in the management of ovarian tumours use CA-125 as surrogate marker for response and prognostication.

7. Conclusion

The changes in CA125 levels were significant in both malignant and benign tumors thus reinforcing the importance of its role as a biomarker in ovarian neoplasms especially in epithelial ovarian cancers.

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