ORIGINAL RESEARCH PAPER

Biochemistry

STUDY BIOCHEMICAL PARAMETER TOTAL PROTEIN AND ALBUMIN IN OVARIAN TUMORS BEFORE AND AFTER CHEMOTHERAPY

KEY WORDS:

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ABSTRACT

Malignant disease has been shown to be associated with low albumin. Albumin has been shown to be a prognostic marker in colorectal cancer, glioblastoma multiforme, gastric cancer and breast cancer. Ovarian cancer patients are more likely to present with poor nutritional status and cachexia. They are more likely to experience rapid changes in their nutritional status and body composition. Studies showed that ovarian cancer patients are more likely to have low serum protein levels and malnutrition. The current study is designed with an aim to explore the changes in Total Protein and Albumin of malignant and benign ovarian tumors pre therapy and post therapy.

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. The pre treatment protein levels in patients with benign tumours were 11.05±6.31 g/dl and post treatment levels were found to be 7.90±3.60 g/dl. (p=0.08) In malignant tumours pre treatment mean levels of proteins was10.38 ± 7.67 g/dl and post treatment level was 7.03 ±0.4.02 g/dl(p =0.001) while the reduction in albumin level post therapy was statistically significant(p<0.0001). A positive correlation was found between CA125 levels and total protein, albumin. The total protein and albumin levels showed a significant reduction in malignant tumors whereas it was not significant in benign tumors

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.

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.

Early ovarian cancer is diagnosed by surgical evaluation of an adnexal mass. The decision to subject a patient to surgical exploration is difficult to make, however. Ultrasonography evaluation of adnexal masses has improved the ability to distinguish patients who should have surgical exploration.

Albumin is produced by the liver and almost 60% is present in the extravascular space. It helps to maintain intravascular oncotic pressure; facilitate transport of substances and acts as a free radical scavenger. Malignant disease has been shown to be associated with low albumin due to inhibitory effect on its synthesis from liver and sequestration in ascites or pleural effusion. Albumin has been shown to be a prognostic marker in colorectal cancer, glioblastoma multiforme, gastric cancer and breast cancer Ovarian cancer patients are more likely to present with poor nutritional status and cachexia due to the metabolic effects of advance stage, high tumour burden, ascites and small bowel obstruction Malnutrition leads to reduced muscle mass and subsequently affecting the functional status of the individual. Patients with ovarian cancer are more likely to experience rapid changes in their nutritional status and body composition. Studies showed that ovarian cancer patients are more likely to have low serum protein levels and malnutrition.

REVIEW OF LITERATURE

Asher, et al estimated Pre operative serum albumin is an independent prongoostic predictor of survival in ovarian cancer. Patients with serum albumin levels of 25g/ltr had median survival of 4.8 months, while levels of more than 35gm/ltr were associated with medium survival of 43.2 months. Serum albumin retained significance as an independent predictor of poor survival on Cox's, Multivariate regression analysis. Along with age. (P<0.001 and FIGO Stage (P<0.001)

Parker D et.al analyzed Serum albumin and CA-125 are as powerful predictors of survivals in Epithelial ovarian cancers..[57] This study included 114 patients of EOC (Epithelial Ovarian Cancer). Linear increase in risk was observed with high log CA-125 level (P<0.0001) and with Low albumin (P<0.0001). In late stage patients (Stage III & IV) Albumin was the best predictor of survival (P=0.0006). CA-125 and albumin can be used to identify prognostic sub groups independently of stage. Albumin alone can be used as a predictor of survival. A classification of patients with 3 sub groups based on serum albumin of ≥ 41g/ltr, 35-40g/ltr and 34g/ltr provides clear separation of survival curves in this group of patients.

AIMS AND OBJECTIVES

- To explore the changes in the biochemical profile Total Protein and Albumin of malignant and benign ovarian tumours pre therapy and post therapy.
- To explore the differences in the biochemical profile Total Protein and Albumin between healthy individuals and patients with ovarian tumours.

MATERIALS AND METHODS

The present study was conducted in the Department of Biochemistry, Rangaraya Medical College, Kakinada, Andhra

Pradesh. The present study was undertaken to study the various changes in the biochemical parameters in the serum of patients with ovarian tumors before and after therapy (Surgery and/or chemotherapy). 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.

Serum total proteins were estimated by Biuret method
Serum albumin levels were estimated by BCG dye binding method CA 125 estimated by CLIA

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.

Demographic profile of Patients with Tumors 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		
	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	23	79.3
	Pts who had 5 cycles	2	6.9
	Pts who had 3 cycle	3	10.3
	Pts who had 1 cycle	1	3.5
Surgery	Complete	35	87.5
	Incomplete	3	7.5
	No surgery	2	5.0
Patients with Malignant tumours (N = 29)	Chemotherapy only	2	6.9
	Neoadjuvant chemotherapy +Surgery	1	3.5
	Surgery +Adjuvant Chemotherapy	26	89.6

Biochemical 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
Total protein(g/dl)	8.63	8.55	8.6±0.16	8.63±1.05	5.2-11.0
Albumin (g/dl)	4.58	4.75	4.58±0.14	4.58±0.92	2.50-6.50

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

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range
Total protein (g/dl)	Pre	10.56	8.20	1.14	7.24	6.00-38.00
	Post	7.27	5.95	0.61	3.88	3.30-20.0
Albumin (g/dl)	Pre	4.36	3.35	0.38	2.45	2.00-14.80
	Post	2.88	2.65	0.22	1.39	1.00-9.80

Changes in Pretreatment and post treatment biochemical parameters in benign ovarian tumours

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range	P- Value
Total protein (g/dl)	Pre	11.05	9.50	1.90	6.31	6.4-28	0.08
	Post	7.90	7.60	1.08	3.60	5-18	
Albumin (g/dl)	Pre	3.90	3.30	0.59	1.99	2-9.6	0.009
	Post	2.66	2.90	0.28	0.95	1-4.6	

Changes in Pretreatment and post treatment biochemical parameters in malignant ovarian tumours

Parameters	Pretreatment/Post treatment	Mean	Median	± SEM	± SD	Range	P- Value
Total protein (mg/dl)	Pre	10.38	7.32	1.42	7.67	6-38	**0.001**
	Post	7.03	5.90	0.74	4.02	3.3-20.0	
Albumin (mg/dl)	Pre	4.56	3.60	0.50	2.66	2.8-14.80	**<0.0001**
	Post	2.96	2.50	0.29	1.56	1.5-9.80	

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

Parameters	Pretreatment/ Post treatment	Mean	Median	± SEM	± SD	Range	P- Value
Total protein(mg/dl)	Pre	10.65	8.4	1.17	7.32	6-38	**<0.0001**
	Post	7.29	5.9	0.63	3.93	3.3-20.0	
Albumin (mg/dl)	Pre	10.65	8.4	1.17	7.32	6-38	**<0.0001**
	Post	2.88	2.6	0.22	1.41	1-9.8	

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

Parameters	Controls/ Tumours	Mean	Median	± SEM	± SD	Range	P-Value
Total protein (mg/dl)	Controls	8.63	8.55	0.16	1.05	5.2-11.0	0.09
	Ovarian tumours	10.56	8.20	1.14	7.24	6.00-38.00	
Albumin (mg/dl)	Controls	4.58	4.75	0.14	0.92	2.50-6.50	0.59
	Ovarian tumours	4.36	3.35	0.38	2.45	2.00-14.80	

Correlation between CA125 and other biochemical parameters in Benign Ovarian tumours

Parameter 1	Parameter 2	R value	Correlation
CA125	Total protein	0.48	Positive
CA125	Total albumin	0.21	Positive

Note: Correlation is stronger when r value is closer towards +1 & -1; Correlation done by Spearman's test.

Correlation between CA125 and other biochemical parameters in Malignant Ovarian tumours

Parameter 1	Parameter 2	R value	Correlation
CA125	Total protein	0.48	Positive
CA125	Total albumin	0.49	Positive

Note: Correlation is stronger when r value is closer towards +1 & -1; Correlation done by Spearman's test

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 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.

Platinum based chemotherapy using cisplatin or carboplatin in combination with paclitaxel is the standard adjuvant therapy in ovarian cancers. [77,78] 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 biochemical parameters in pre and post therapy in both benign and malignant ovarian tumours. Moreover, we sought to study the differences in these parameters between the afflicted patients and the healthy controls. We also did a subset analysis to study the correlation of other biochemical parameters with the main tumour marker CA-125 in patients with both benign and malignant ovarian tumours.

The pre treatment protein levels in patients with benign tumours was 11.05±6.31 g/dl and post treatment levels were found to be 7.90±3.60 g/dl. (p=0.08) while the serum albumin level changed significantly (P<0.009) [table-9 & figure-10] .In malignant tumours pre treatment mean levels of proteins was10.38 ± 7.67 g/dl and post treatment level was 7.03 ±0.4.02 g/dl(p =0.001) while the reduction in albumin level post therapy was statistically significant(p<0.0001). The elevated pretreatment serum protein and albumin levels in our cohort of patients was quite surprising and in contrast to the observations in various studies in which patients ovarian tumours tend to be malnourished and cachexia and hence tend to have low protein and albumin levels.

Cancer cachexia in ovarian tumours is a manifestation of advance stage disease wherein patients tend to have gross third space collections (pleural effusion or gross ascites). In our study, none of the 29 patients with ovarian cancer had advance stage disease (stage III or IV) and were in good general condition (karnofsky performance score of 80 or above). None of the patients presented with ascites or pleural effusion which could be the reason for normal protein or albumin levels. However, the protein and the albumin levels decreased significantly after chemotherapy which could be attributed to the catabolic state of the body as a result of excessive emesis following therapy with aggressive anti neoplastic drugs which literally results in loss of appetite in these patients leading to malnutrition and reduction in serum protein and albumin.

We also tried to see the correlation between CA-125 protein and albumin both in benign and malignant ovarian tumours. A positive correlation was found between CA125 levels and total protein, albumin However, in benign tumours, a positive correlation was found between CA125 and total protein and albumin levels .However none of them were statistically significant to draw any tangible conclusions (r-value did not straddle unity) either in benign or in malignant tumours

CONCLUSION

The study of biochemical parameters of ovarian tumors carried out in Rangaraya Medical College with the objective of exploring the changes in the biochemical profile of malignant and benign ovarian tumors pre and post therapy. The total protein and albumin levels showed a significant reduction in malignant tumors whereas it was not significant in benign tumors. This could be due to catabolic state of the body due to chemotherapy induced cancer cachexia and/or malnutrition in our patients.

A positive correlation was found between CA125 levels and total protein, total albumin in both malignant and benign tumors. However none of them were statistically significant.

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