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Biochemistry Section

CA 125 Elevation: A Descriptive Etiological Study

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ABSTRACT

Introduction: CA 125 (Cancer/Carbohydrate antigen 125) is a surface antigen expressed mostly by the ovarian cancer cells. Hence, it is widely used as a tumour marker for detection and monitoring the progression of such cancers. CA 125 is also expressed by cells of different tissues such as pleura, pericardium, Mullerian epithelium, peritoneum etc.

Objective: To identify the different causes leading to elevation of CA 125 and to estimate the elevation of CA 125 in ovarian and non-ovarian causes.

Materials and Methods: A total of 1800 patients testing for CA 125 during the time period January 2011 to December 2013in Kasturba Medical College constituent hospitals, Mangalore were screened. Out of these, OPD patients and in-patients with CA 125 < 35 U/mL were excluded and remaining 236 in-patients were included as the study subjects. Patients were categorized into four groups based on CA 125 level as Group I(35 – 200 U/mL), Group II (201 – 500 U/mL), Group III (501 – 1000 U/mL) and Group IV (>1000 U/mL). To find association of CA 125 with age, patients were stratified into 3 groups based on their age as Group A (15-35 years), Group B (36-55 years) and Group C (≥ 56 years). Parameters like age, BP, hemoglobin, CA 125,renal profile and diagnosis of all the patients were evaluated.

Results: Out of 236 patients 54.7% were suffering from malignant ovarian diseases, 31.3% benign ovarian disease, 12% non-gynecological diseases and 2% from gynecological diseases of non-ovarian origin. Mean age for malignancies was 55 ± 10.6 years for benign diseases was 34±12.7 years. Incidence of malignancy among the 4 groups (based on CA 125 level) was 34.4%, 48.8%, 68.7% and 91.6% respectively. Increase in both age and CA 125 levels was highly significant in patients suffering from ovarian malignancies when compared to those with benign ovarian diseases ($p<0.001$).Difference in CA 125 levels was also statistically significant between malignant and non gynaecological disorders and between benign ovarian and non gynaecological disorders as well ($p<0.001$).

Conclusion: In spite of higher levels of CA 125 in ovarian carcinoma cases compared to other diagnosis in our data, results confirm the high false positive rate and non-specificity associated with CA 125 as a biomarker as it was seen to increase in numerous other diseases.

Keywords: Antigen, Benign ovarian disease, Malignant ovarian disease

INTRODUCTION

CA 125 (encoded by MUC 16 gene) is a member of the mucin (MUC) family of high molecular weight glycoproteins whose function is to provide lubrication and maintain hydration on the luminal surface of epithelial cells thus being protective in nature. CA 125 is a tumour antigen widely known for its role in diagnosing ovarian cancers as it is expressed on the surface of cancer cells of the ovaries. It also helps in monitoring the growth of such cancers [1].

CA 125 being a soluble glycoprotein undergoes proteolytic cleavage in response to mechanical stress or inflammation and is released from the cell surface into the bloodstream or other body fluids like pleural fluid (as in pleural effusion), peritoneal fluid (as in ascites) etc., [2]. It is a large membrane-bound MUC and is also normally expressed by cells of different tissues like pleura, pericardium, peritoneum, and Mullerian epithelium (all are derived from ceolomic epithelium) [3].

CA 125 (MUC 16) was originally considered to be a specific tumour marker for carcinomas of ovarian origin. However, recent studies have reported detectable levels in blood of patients suffering from non-ovarian malignancies such as colorectal adenocarcinoma, pancreatic and gastric carcinoma. MUC16 thus plays an important role in at least some of the adenocarcinomas of GIT and its elevation suggests poor survival in such patients [4]. Several studies have also shown increased levels of this biomarker in infectious diseases like tuberculosis and benign disorders like liver disease, congestive heart failure, endometriosis etc. Increased levels were seen even in physiological conditions like pregnancy thus necessitating the need to compare and contrast the levels of CA 125 in various etiologies [5].

AIMS

1. To identify the different causes leading to increased levels of CA 125 in serum.
2. To compare this increase in CA 125 with different ovarian and non-ovarian diseases and also benign and malignant neoplasms.

MATERIALS AND METHODS

This is a retrospective descriptive study. Data for the study was collected from the medical records of in-patients (serum CA 125 levels >35U/ml) at KMCH-AC and KMCH-AT during the time period January 2011 to December 2013.The study was approved by Institutional Scientific Committee. All patients with their diagnosis confirmed by histopathology were included in the study. However, patients with incomplete data were excluded.A total of 1800 people underwent CA 125 test in our lab during the study time period, out of which 1262 people had levels < 35 U/l and were excluded from the study. Out of 538 people with CA 125 levels > 35U/l, 236 people were in-patients, and were included in the study. Broadly patients were categorized into four groups based on their diagnosis as malignant ovarian, benign ovarian, non- gynecological, non-ovarian gynecological causes. Based on CA 125 levels they were categorized into four groups as Group I (35 – 200 U/mL), Group II (201 – 500 U/mL), Group III (501 – 1000 U/mL) and Group IV (>1000 U/mL). To find out the association of age of the patient with CA 125 levels, these patients were stratified into 3 groups based on their age as Group A (15- 35 years), Group B (36-55 years) and Group C (≥ 56 years).

STATISTICAL ANALYSIS

Descriptive statistical analysis was done using SPSS version 17.5. Data with continuous measurements were expressed as Mean ± S.D. Categorical measurements were expressed as number (%). Intergroup comparison of mean age and CA 125 levels was done using ANOVA and Kruskal Wallis test respectively. Chi square analysis was used to find the association between elevated levels of CA 125 with the diagnosis. The p-value < 0.05 was considered statistically significant.

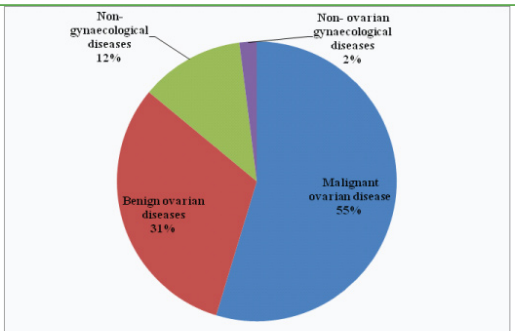
RESULTS

In the present study age of the patients ranged from 16 to 86 years with a mean age of 47 years. [Table/Fig-1] shows the baseline characteristics of study population. Prevalence of different causes of elevation of CA 125 among the study population is shown in [Table/Fig-2]. Out of 236 patients 129 (54.7%) were diagnosed with malignant ovarian diseases, 74 (31.3%) with benign ovarian disease, 28 (12%) with non-gynecological diseasesand 5 (2%) were suffering from gynecological diseases of non-ovarian pathology. [Table/Fig-3] shows mean age and CA 125 values in four groups. Age of the patients suffering from benign ovarian disorders was significantly different from ovarian malignancies and non ovarian disorders as well (p<0.001). Significant increase in CA–125 levels was seen in ovarian malignancies when compared to benign ovarian diseases (p<0.001). There was also a significant difference in CA 125 levels in the non gynaecological disorders when compared to both benign and malignant ovarian disorders (p<0.001).

[Table/Fig-4] shows the distribution of benign and ovarian diseases among the groups stratified on the basis of CA 125 levels. Incidence of malignancy among the 4 groups was 34.4%, 48.8%, 68.7% and 91.6% respectively. It shows that percentage of patients diagnosed with ovarian cancer increased significantly with increase in CA 125 levels where as percentage of benign ovarian diseases decreased significantly with an increase in CA 125 levels. However, other causes did not show any significant changes with CA 125.

	Group I (35-200 U/mL)	Group II (201–500U/mL)	Group III (501-1000 U/mL)	Group IV (>1000 U/mL)
Age	42.5±14.9	47.88±15.5	53.5±15.4	56.54±13.18
SBP (mm/Hg)	121.6±12.4	121.8±11.2	130.81±14.9	127.4±16.8
DBP (mm/Hg)	79±6.17	77.9±5.8	82.43±8.13	81.4±8.6
Hb (g/dL)	11.12±1.55	11.34±1.77	11.34±1.15	11.06±1.5
Urea (mg/dL)	20.5±7.6	20.37±10.34	19.71±7.19	22.06±9.5
Creatinine (mg/dL)	0.75±0.61	0.78±0.22	0.7±0.24	0.77±0.74
ESR (mm/hr)	30.3±19.6	48.38±32.2	44.06±28.43	45.8±23.9
RBS (mg/dL)	126.9±51	136.8±62.3	125.3±34.8	120.6±34.9
CA 125 (U/mL)	86±46.8	319.7±87.9	695.2±125.8	3164±2149
DM (n)	11	3	3	9
HTN (n)	14	4	3	10
Infertility (n)	8	7	2	1
Expired (n)	1	0	2	1

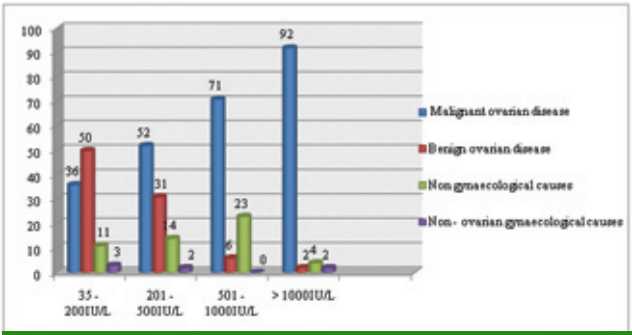
[Table/Fig-1]: Baseline characteristics of study groups based on CA 125 levels.



[Table/Fig-2]: Prevalence of different etiologies among the study population.

Type of disease	n (No. of Patient)	Age (in years)	CA 125 (U/ml) (Normal : 0 - 35 U/ml)
Malignant ovarian diseases	129	55.3 ± 13.1	1580.8 ± 2977.8
Benign ovarian diseases	74	33.8 ± 8.4	146.69 ± 216.2
Non- gynecological diseases	28	49.3 ± 18.4	406.7 ± 541.9
Non- ovarian gynecological diseases	5	52.8 ± 17.5	542.9 ± 951.8

[Table/Fig-3]: Mean age and CA 125 values in four groups based on diagnosis.



[Table/Fig-4]: Distribution of disease etiologies among the groups based on CA 125 levels.

DISCUSSION

Markedly increased levels of CA 125 in ovarian malignancies in our study emphasize the importance of CA 125 in malignant ovarian diseases. The fact that serum CA 125 is increased consistently in advanced epithelial ovarian cancers can add to its utility as a marker for monitoring the progression of disease, response to chemotherapy and as a prognostic indicator in such patients [6].CA 125 cannot be used alone for screening ovarian carcinoma as it not highly sensitive enough for detecting all cases of early-stage ovarian cancer [7]. However, increase in serum levels of CA 125 is not restricted to ovarian malignancies. Studies have shown increased levels in non-ovarian neoplasms like pancreatic and gastric adenocarcinomas, carcinomas of lung, liver etc., [4]. Increase is also seen in physiological conditions like pregnancy, infectious diseases like tuberculosis and in various benign conditions like liver diseases, endometriosis, congestive heart failure etc., [5].

Our study results were in agreement with the above findings of other studies. In the present study population CA 125 was found to be elevated in other carcinomas like gastric cancer, breast cancer with peritoneal metastasis, Ca ascending colon, cervix and lung, chorio-carcinoma, primary peritoneal carcinomatosis and retroperitoneal metastatic deposits. It was also elevated in benign conditions like endometriosis, leiomyoma, abdominal TB, fibroid uterus, decompensated chronic liver disease, adenomyosis and mesenteric cyst. Due to its non-specificity, clinical interpretation of elevated CA 125 should be implemented with caution. However, our study results also reveal highly increased levels in ovarian malignancies as compared to the increase in benign ovarian diseases and other causes of CA 125 elevation. This difference in increase was found to be highly significant statistically and in agreement with the results of a study conducted by Radhika et al., [8]. In this study malignant ovarian disease was mainly seen in older age group compared to benign (mean age of 55 and 33 respectively) which is in agreement with the study conducted by Wasim et al., [9].

Among male patients hepatic cirrhosis was found to be the most frequent cause of CA 125 elevation. As CA 125 is also expressed in epicardium, diseases of heart may also lead to increased levels in blood [2]. Kouba et al., suggested that CA 125 can be used as a prognostic indicator in patients diagnosed with transitional cell carcinoma of the bladder undergoing radical cystectomy [10]. Its use as a biomarker for lung cancer, as well as its strong predictive significance in the diagnosis of peritoneal metastasis in gastric cancer patients has also been reported [11-13]. Various other studies have reported high levels of CA 125 in lymphoma, melanoma, malignant diseases of pancreas, liver, breast, colon, and rectum [14-16].

In a routine clinical training, a female patient presenting with increased levels of serum CA 125 and ascites is presumed to be ovarian cancer (advanced stage). However, in a study conducted by Bae et al., to determine the importance of serum CA 125 in the differential diagnosis of tuberculous peritonitis and ovarian cancers in a TB endemic region, it was concluded that tuberculous peritonitis should also be kept in mind while evaluating a female patient with ascites and elevated serum CA 125 [15]. Ovarian cancer patients with peritoneal advancement present with highly nonspecific symptoms such as pelvic or abdominal pain, bloating, indigestion and abdominal distention [16]. It is thus challenging to diagnose a peritoneal TB because of its non-specific presentation (symptoms, radiographic, pathologic, and laboratory findings). Because of vague symptoms, it mimics ovarian cancer and other non-tuberculous granulomatous diseases [17]. Unnecessary laparotomy can be avoided in such cases if diagnosed properly [15].

The causes for increase of CA 125 concentration in so many different diseases are still not fully understood. As per existing knowledge, this mucin may be produced continuously in small amounts by cells of different origin [18]. CA 125 being a soluble glycoprotein undergoes proteolytic cleavage in response to stimulus like inflammation or even mechanical stress and thus released into the bloodstream or other body fluids. As the inflammatory diseases progress, CA 125 levels may rise due to stimulation of body's immune system and activation of cytokines and other inflammatory factors [19].

Therefore, further research to find new specific biomarkers for early detection and monitoring of ovarian cancer is in progress [20].

CONCLUSION

Serum CA 125 levels were significantly higher in ovarian malignancies when compared to benign ovarian diseases and other non-ovarian etiologies in our data. We also found positive association between age and CA 125 in ovarian diseases. Ovarian malignancies were seen mainly in older age group compared to the benign disorders. CA 125 cannot be used as an ideal screening test for ovarian carcinoma as it lacks sensitivity and specificity. But it is still a good marker for monitoring the prognosis of patients already diagnosed with ovarian carcinoma. Its role as a marker for screening ovarian cancers is still under consideration and requires larger prospective studies.

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