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TUMOR MARKERS;

Efficacy of CA-125, CEA, AFP, & Beta HCG
An institutional based descriptive & prospective study in diagnosis of ovarian malignancy

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ABSTRACT… Object: Analysis of serum tumor markers CA-125, CEA, AFP, & ß-HCG in patients with ovarian malignant tumors and correlation of their serum levels with histological types. **Study Design:** Institution based descriptive and prospective study. **Place & Duration:** Department of Pathology, Liaquat University of Medical & Health Sciences, Jamshoro from January 2009 to June 2011. **Material & Methods:** One hundred cases, diagnosed as ovarian malignant tumor on H&E staining were selected for study & measurement of serum CA-125, CEA, AFP, & ß-HCG preoperatively and postoperatively in each case. **Results:** Out of 100 ovarian cancers diagnosed on H&E stain 33 were serous cystadenocarcinoma, 29 mucinous adenocarcinoma, 19 germ cell tumors and 15 sex-cord stromal tumors, 1 endometroid carcinoma, 1 brenner tumor, 1 clear cell carcinoma and 1 case of NHL. Increased level of CA-125 was seen preoperatively in 33/33 cases of serous cystadenocarcinoma and 24/29 cases of mucinous adenocarcinoma. Surprisingly increased levels were also seen in 10/19 germ cell tumor and 8/15 in sex-cord stromal tumors. CEA is raised in mucinous tumors. AFP & ß-HCG were raised in germ cell tumors & sex cord-stromal tumors. Serum tumor marker levels were declined following appropriate therapy of the tumors. **Conclusions:** Serum tumor markers are useful and important for the detection of ovarian tumors. They may also help in assessment of response to specific treatment, prognosis & follow up of patient.

Key words: CA-125, Carcinoembryonic antigen (CEA), Alpha fetaprotein (AFP)

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INTRODUCTION

Ovarian cancer posed the greatest challenge amongst gynecological malignancy. It is 2nd most common malignancy in female reproductive system[1]. The worldwide incidence of ovarian cancer is 192.4, mortality 114.2, & prevalence is 507.5 per 100,000 persons per year[2]. Incidence has been rising about 1-2% per year in several countries[3]. A female's risk at birth of having ovarian tumor sometime in her life is 6.0-7.0%, of having ovarian cancer is almost 1.5% and dying from ovarian cancer is 1.0%[4]. There is considerable variability in the incidence & mortality of cancer amongst different racial groups. Blacks are more likely to develop cancer and have higher mortality than whites, Asians & American Indians, or Hispanics[5]. Geographical difference in cancer incidence & mortality is generally lower for Asian & African countraries[6]. Ovarian cancer is 2nd to 4th most common leading cause of death from gynecologic malignancy in Pakistan. Its mortality ranks 2nd to 5th in various studies[7,8,9,10]. In United States it accounts for 4% of all cancers in women & 5% of estimated cancer deaths[11].

Epithelial ovarian cancer accounts for about 90% of ovarian malignancy. They are of three histological type based on differentiation of neoplastic epithelium; serous, mucinous and endometrioid tumors.

The main presentation is abdominal distensions and pain in abdomen is next common complaint[12]. About 20% of patient have positive family history of

ovarian cancer[13]. Ovarian caner is predominantly a disease of postmenopausal age group (>70yreas); in Pakistan ovarian cancers are seen in early age, where mean age is in between 40-45[14]. 30 % of all ovarian neoplasm occurring during childhood and adolescence are malignant,[15] generally originating from germ cell line.

Although etiology remains unknown, hormonal, environmental and genetic factors play an important role in the development of ovarian cancer. In Pakistan various risk factors such as early menarche, late menopause, nulliparity, lack of lactation are uncommonly observed[16]. Younger age at presentation and higher frequency of positive family history are two unusual features of Pakistani patient with ovarian cancer.

Majority of patients had stage III –IV disease at the time of diagnosis, frequency varies 56%-88%[16,13,15] which is responsible for higher mortality with the disease. Early diagnosis is the only way to reduced mortality.

Various tumor markers are available which can help in diagnosis, response of therapy, prognosis and early detection of recurrence. Amongst them cancer antigen (CA-125), Carcinoembryonic antigen (CEA), Alpha fetoprotein (AFP), & Beta-Human chorionic gonadotrophin (ß- HCG) are important and reliable serum biomarkers for early detection and prognostification of ovarian cancer[17].

CA-125 is the gold standard tumor marker in ovarian cancer. Serum level of CA-125 is used to monitor response to chemotherapy, relapse, & disease progression in ovarian cancer patients[18]. Both AFP and ß-HCG play crucial roles in the management of patients with germ cell tumors. Their levels were elevated in 85 % of patient with these tumors[19].

The aim of present study was to evaluate the efficacy of CA-125, CEA, AFP and ß-HCG in diagnosis and response to therapy in patient with ovarian cancer.

MATERIAL AND METHOD

This study was carried out in Department of Pathology, Liaquat University of Medical & Health Sciences, Jamshoro from January 2009 to June 2011. Patients diagnosed as ovarian cancer on clinical and radiological grounds were selected. One day before surgery we collected 5cc of blood with BD syringe and serum were separated by centrifuged at 3000 rpm for 10 minutes and transfer 500ul serum in aliquots for storage at -20c. Another sample was collected during first week after surgery.

100 samples were selected which were morphological proven ovarian cancer & examined for CA125, CEA, AFP, & ß-HCG levels for preoperative and post operative status. They were estimated by solid phase sandwich elecsys method by using commercially available kits (Roche).

Calculations

The analyzer automatically calculates the concentration of each sample in U/ml. For quality control we used Elecsys precicontrol tumor marker 1 & 2.

RESULTS

A total number of 100 patients with histologically confirmed malignant ovarian tumors were included in this study. The preoperative and postoperative analysis of serum of 100 included cases for CA-125, CEA, AFP, & ß-HCG were carried out. Their histological diagnoses were serous cystadenocarcinoma (33%), mucinous cystadenocarcinoma (29%), germ cell tumors (19%), sex-cord stromal tumors (15%) and other tumors (4%).

CA-125 was seen increased preoperatively in 33/33 cases of serous cystadenocarcinoma, 24/29 cases of mucinous cystadenocarcinoma, 10/19 cases of germ cell tumors, 8/15 sex-cord stroma tumors and negative in Brenner tumor, endometrioid tumor, clear cell carcinoma and NHL. While postoperatively, CA-125 level found decreased (below the level of 50 IU/ml) in 33/33 of serous cystadenocarcinoma, 23/24 of mucinous

cystadenocarcinoma, 10/10 germ cell tumor and 8/8 in sex-cord stromal tumors. These results indicate significant decline of CA-125 in ovarian cancers following surgical removal / debulking and other treatment.

CEA was seen increased preoperatively only in mucinous cystadenocarcinoma, which was decreased postoperatively (Table II a & b).

AFP was seen increased preoperatively in all cases of germ cell tumors, but decreased postoperatively in all except two cases of germ cell tumor but below levels of 50 IU/ml which is insignificant for disease (Table-III a & b).

ß-HCG was seen increased preoperatively in 19/19 cases of germ cell tumors and 14/15 cases of sex-cord stromal tumors but seen decreased in all cases postoperatively except one case of sex-cord stromal tumor (Table-IV a & b) which indicate its significance.

Type of malignant ovarian tumor	More than 35.0	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	1	5	10	9	3	5	33
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	1	9	11	2	1	-	24
Germ cell tumor	4	3	2	1	-	-	10
Sex-cord stromal tumor	5	3	-	-	-	-	8
Others NHL	-	-	-	-	-	-	-

Table-I(a). Results of preoperative CA-125 level in each histological type of malignant ovarian tumors (N-100). (Normal range upto 35.0 IU/ml)

Type of malignant ovarian tumor	More than 35.0	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	-	-	-	-	-	-	-
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	1	-	-	-	-	-	1
Germ cell tumor	-	-	-	-	-	-	-
Sex-cord stromal tumor	-	-	-	-	-	-	-
Others NHL	-	-	-	-	-	-	-

Table-I (b). Results of postoperative CA-125 level in each histological type of malignant ovarian tumors (N-100). (Normal range upto 35.0 IU/ml)

Type of malignant ovarian tumor	More than 10	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	-	-	-	-	-	-	-
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	15	9	4	1	-	-	29
Germ cell tumor	-	-	-	-	-	-	-
Sex-cord stromal tumor	-	-	-	-	-	-	-
Others NHL	-	-	-	-	-	-	-

Table-II (a). Results of preoperative CEA level in each histological type of malignant ovarian tumors (N-100). (Normal range: up to 10ng/ml)

Type of malignant ovarian tumor	More than 10	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	-	-	-	-	-	-	-
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	-	-	-	-	-	-	-
Germ cell tumor	-	-	-	-	-	-	-
Sex-cord stromal tumor	-	-	-	-	-	-	-
Others NHL	-	-	-	-	-	-	-

Table-II (b). Results of postoperative CEA level in each histological type of malignant ovarian tumors (N-100). (Normal range: up to 10 ng/ml)

DISCUSSION

This study is an update on subject, which correlate the histological diagnosis of ovarian tumors with results of serological tumor marker. Ovarian cancers were one of the most common and most lethal diseases in women throughout the world; its incidence is even high in developed countries of world[20]. In this study CA-125 is seen more specific tumor marker for serous cystadenocarcinoma. CEA is significant in mucinous adenocarcinoma. While AFP and ß-HCG are more important for germ cell and sex-cord stromal tumors, indicate their significance in diagnosis of ovarian cancers. Their postoperative declines indicate their importance in management, prognosis, & recurrence.

Serum tumor markers CA-125 was important indicators of the epithelial ovarian cancers; similar results reported by Mani R et al. It was more specific for serous cystadenocarcinoma. Similar findings were observed in the study of Mehboob S. et al[21]. The next common group of malignancies included mucinous tumors; they were also associated with marked elevations in serum CA-

Type of malignant ovarian tumor	More than 7.02	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	-	-	-	-	-	-	-
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	-	-	-	-	-	-	-
Germ cell tumor	4	6	5	3	1	-	19
Sex-cord stromal tumor	1	5	4	4	1	-	15
Others NHL	-	-	-	-	-	-	-

Table-III (a). Results of preoperative AFP level in each histological type of malignant ovarian tumors (N-100). (Normal range: upto 7.02 IU/ml)

Type of malignant ovarian tumor	More than 7.02	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	-	-	-	-	-	-	-
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	-	-	-	-	-	-	-
Germ cell tumor	2	-	-	-	-	-	2
Sex-cord stromal tumor	-	-	-	-	-		
Others NHL	-	-	-	-	-	-	-

Table-III (b). Results of postoperative AFP level in each histological type of malignant ovarian tumors (N-100). (Normal range: upto 7.02 IU/ml

125 values, as well as CEA. Similar findings were observed in the study of Mani R et al.

The value of the tumor marker dropped significantly following appropriate treatment. In this way it is proved to be having a good significance in early diagnosis as well as prognostic significance.

In this study we have further observed the increased serum CA-125 level is not only raised in epithelial ovarian cancers, but also in germ cell & sex cord/stromal tumors.

The next common category of malignant ovarian tumors comprised of germ cell and sex-cord stromal tumors. These were associated with marked elevation serum of AFP and ß-HCG markers. Similar findings were reported by Mani R et al. The levels of these tumor markers dropped significantly following appropriate treatment.

Combination of CEA, AFP and ß-HCG in malignant ovarian may give more effective result than using a single biomarker.

Type of malignant ovarian tumor	More than 5.3	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	-	-	-	-	-	-	-
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	-	-	-	-	-	-	-
Germ cell tumor	-	6	2	3	-	8	19
Sex-cord stromal tumor	1	3	1	2	1	6	14
Others NHL	-	-	-	-	-	-	-

Table-IV. (a). Results of postoperative ß-HCG level in each histological type of malignant ovarian tumors (N-100). (Normal range: upto 5.3 mIU/ml)

Type of malignant ovarian tumor	More than 5.3	More than 50	More than 100	More than 200	More than 300	More than 400	Total
Surface epithelial tumors Serous cystadenocarcinoma	-	-	-	-	-	-	-
Brenner Tumor	-	-	-	-	-	-	-
Endometrioid carcinoma	-	-	-	-	-	-	-
Clear cell carcinoma	-	-	-	-	-	-	-
Mucinous adenocarcinoma	-	-	-	-	-	-	-
Germ cell tumor	1	-	-	-	-	-	1
Sex-cord stromal tumor	-	-	-	-	-	-	-
Others NHL	-	-	-	-	-	-	-

Table-IV. (b). Results of postoperative ß-HCG level in each histological type of malignant ovarian tumors (N-100). (Normal range: upto 5.3 mIU/ml)

CONCLUSIONS

Ovarian malignancy is a serious disease, affecting women of all age group. Majority of the patients present in advance stage of disease, therefore prognosis is poor and mortality rate is high. Early detection and appropriate investigation may help to reduce the morbidity and mortality. Clinical, Histological examination and serum ovarian tumor marker may help in the diagnosis, prognosis and treatment of ovarian malignancies.

SUGGESTION

Patients diagnosed as ovarian malignancies either as clinical or histological basis are strongly recommended for serum ovarian tumor markers, for diagnosis of bulk of ovarian tumors. These tumor markers may help oncologist / clinicians for diagnosis, prognosis and treatment of patients.

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