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THE RELATIONSHIP BETWEEN TUMOR MARKERS AND ALBUMIN WITH THE ASCITES EXISTENCE IN MALIGN EPITHELIAL OVARIAN TUMORS

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Abstract

Ovarian cancer is the most lethal and the second most frequently seen gynecologic cancer in developed countries. Most of them takes origin from epithelial surface of ovary. At the time of diagnosis, ascites is determined in one third of patients. In this study our aim is to investigate the relationship between ascites, tumor markers and plasma albumine levels.

Introduction

Ovarian cancer is the most lethal and the second most frequently seen gynecologic cancer in developed countries. Majority of ovarian tumors develop from the surface epithelial and usually seen in postmenopausal women [1].60% of all ovarian carcinomas are found to be in International Federation of Obstetrics and Gynecology (FIGO) stage 3 or 4 disease during the diagnosis.Recent studies have evaluated various panels of circulating biomarkers in ovarian cancer patients[2,3].

CA 125 is an antigenic epitope of heavy molecule weighed glycoprotein and it is secreted from the derivatives of cholomic epithelial [4]. It is found inside the normal ovarian tissues and in endometrial, endocervical, pleural and peritoneal epithelial derivatives[5]. Not just being elevated in malign ovarian tumors but the high level of CA 125 along with the existence of ascites can be determined in benign diseases as well [6].
Other known markers in ovarian cancers are CA 19-9 and CEA (Carcinoma Embryonic Antigen). CA 19-9 can be determined highly in gastrointestinal and lung cancers other than ovarian cancers.On the other hand CEA can be elevated in gastro intestinal, lung and breast cancers. İn a study conducted by Gadducci et al. , the level of CA 19-9 in 90 epithelial ovarian cancer patients and 254 patients with benign ovarian pathology was measured preoperatively. Sensitivity of CA 19-9 (“cut-off, 40 U/m) was found to be 35.6% and specificity was found to be 81.1% for the epithelial ovarian cancer (EOC) detection [7]. CA 19-9 carries high sensitivity for mucinosis type ovarian carcinoma. CA 19-9 > 40 U/m was determined in 35.6% of patients with epithelial ovarian cancer and 83.3% of them has mucinosis histological type .

Alpha fetoprotein (AFP) is a molecule being structured as single chained polypeptide and it is a type of oncofetal protein generated by endodermal sinus tumor, embryonic carcinoma, polyembryo and immature teratoma. AFP is not only specific to the germ celled ovarian tumors but it is usually determined in benign lung cancers and gastrointestinal system cancers as well [8].

Albumin is the most widely found protein in blood plasma.Aside from assuring the oncotic pressure, it has many other functions such as carrying fat-soluble substances and connecting free oxygen radicals. While decrease in serum albumin levels can be observed in such liver diseases as cirrhoses; albumin levels may decrease in long term chronic diseases ,malnutrition and malignancies.
Ascites is the accumulation of liquid in the peritoneal spaces. The etiology of ascites is malignancy in 10% of the patients and most often them is primer ovarian cancer [3]. Malign ascites can be developed through direct invasion

to peritonea as in the peritoneal carcinomatosis or it can be secondary depending on the local biology of the tumor or vena cava compression.Majority of epithelial ovarian cancers are diagnosed by findings such as chronic pelvic pain, abdominal swelling and/or constipation.Sometimes EOC diagnosis is done while ascites etiology is being examined. Ascites existence containing the malign cell in ovarian cancer comes across as a finding that changes the stage. Therefore, ascites existence is essential in determining the prognosis of the patient before staging. With the exception of highly invasive procedures such as biopsy and surgery, the evaluation of circulating biomarkers offers the most definitive means of distinguishing early stage EOC from advanced stage disease.
The aim of the present study was to analyze the relationship between preoperative CA 125, CA 19-9,AFP, CEA and albumin levels with the malign ascites existence in epithelial ovarian cancers.

Materials and methods

This research includes 80 patients operated due to malign epithelial ovarian tumor in gynecology and obstetrics department of İzmir Ege Gynecology and Obstetrics Teaching and Research Hospital , between 2004 and 2008.Patients with a history of cancer ,medical diseases that causes ascites like cirrhosis , congestive heart failure and metastatic ovarian cancers like krukenberg tumors were excluded ; only patients with primary ovarian cancers were included in the study. All of the 80 patients went through optimal debulking operation and the ascites existence was confirmed through their surgery entries. After the study protocol was evaluated and approved by the Institutional Review Board; tumor markers, albumin levels, ascites cytology and surgery notes of the patients were recorded from the patients' files by the researcher. Tumor markers and albumin levels of 48 cases with intraoperative ascites and 32 cases without ascites were compared. Findings were evaluated with SPSS Version 15 (Chicago, IL).

Non parametric Mann-Whitney U test was used for non-normal distribution. When necessary, the distribution of ovarian surface tumors among the groups was calculated by the utilization of fisher's exact chi-square test. Findings were provided as median (minimum-maximum). And ***P values*** less than ***0.05*** were considered statistically ***significant***.

Results

Ages of the patients which have been included into study were from 29 to 76 years old. Age median values of the patients with and without ascites were respectively 51 and 57; in terms of age there was no statistical significant difference among the two groups.24 of the 48 patient (50%) with ascites had serous adenocarcinoma, 11(22.91%) had mucinous adenocarcinoma, the other 11 (22.91%) had endometrioid adenocarcinoma and the remaining 2 (4.16%) had clear cell tumor. 15 of the 32 patients (46.87%) without ascites had serous adenocarcinoma, 8 (25%) had mucinous adenocarcinoma, 7 (21.87) had endometrioid adenocarcinoma and the final 2 (6.25%) had clear cell tumor. No statistical significant difference was found among the tumor types of the patients with or without ascites (Table 1).

Tumor sizes of the patients with or without ascites are respectively 12.5 and 9.5 according to the median value and no statistically significant difference was found among both groups. The median value of serum albumin level was found to be 3.3 g/dl in cases with ascites and was found to be 3.7 g/dl in cases without ascites.When we compared the patient groups in terms of albumin significant statistical difference was determined among the two groups (p: 0.018). We didn't determine any statistically significant difference when we compared both patient groups' CEA, AFP, CA125 and CA 19-9 values (Table 2).

Conclusion

Ovarian cancer accounts for 4-6% of all cancers among women[9,10].Symptoms of ovarian cancer are not specific to the disease, and they often mimic those of many other more-common conditions, including digestive problems. Patients are commonly being diagnosed with asymptomatic delay until metastasis of the disease. Many risk factors have been identified for ovarian cancer. The best documented of these is the relationship between the number of lifetime ovulatory cycles and ovarian cancer. Events or conditions that suppress ovulation protect women against this malignancy. The biology of ovarian carcinoma differs from that of hematogenously metastasizing tumors because ovarian cancer cells primarily disseminate within the peritoneal cavity[11]. Ascites formation is observed more than 1/3 of the patients and larger portion of them create ascites during the progression [12]. Ascites

formation is most likely associated with intraperitoneal spread of disease.On the other hand, there are two opinions about the underlying mechanism of malign ascites formation [13]. Some authors support the idea that an increase in the capillary permeability, due to active proteins in peritoneal tissues lead to excess peritoneal liquid accumulation. Others inform that the obliteration of diaphragmatic lymphatics from tumor cells cause decrease in protein absorption, which is normally a filter from peritoneal capillary; therefore ascites formation is a triggering factor in pathogenesis [14-15].

Existence of ascites alone has been informed as being a poor prognostic factor in certain studies yet this hasn't been recognized worldly in general [12-16]. Since the existence of malign cell in peritoneal washing liquid or ascites liquid speed up the stage in ovarian cancer , it is an important prognostic factor [17]. In a study of Ayhan et al. it has been informed that ascites is correlated with the spread of tumor and its stage.They informed that ascites is an indirect predictor in the prognosis of the disease [18]. We also targeted to research the connection of ascites between the biochemical tumor markers and albumin.

The most frequently seen histological type of epithelial ovarian cancer is serous adenocarcinoma and the age, it is most diagnosed, is the ages of 50-60. The most observed tumor type in the two groups, which took place in our study, was serous adenocarcinoma and the median age value of both groups was within the 5th decade. When we compared the two groups in terms of their ages and tumor types we found no significant difference between them. Generally, 83% of the epithelial ovarian cancer patients have >35 U/mL CA 125 levels [19]. CA 125 sensitivity is (50%) lower in 1st stage of the disease but it is 90% in 2nd and following stages of the disease and this sensitivity can show changes according to histology [5]. Along with rarely increasing in CEA, AFP and CA 19-9 in EOC; significant increase can be determined in other types of ovarian cancers. When we compared the patients with and without ascites in terms of their CA 125,CEA, AFP and CA 19-9 values, we didn't find any significant differences. Albumin is a protein mostly found in the plasma and plays an important role in establishment of the plasma oncotic pressure. Regular serum albumin concentration in healthy people is between 3.5-5 mg/dl.Albumin levels may decrease in long term chronic diseases ,malnutrition and malignancies.We also found that the median value of serum albumin level was lower in cases with ascites.

Most of the pertinent literature reporting that ascites existence and lower levels of serum albumin are associated with poor survival and advanced stage disease.[20,21,22]İn our study there is no correlation between tumor markers and ascites existence.

As conclusion, tumor markers are not usefull in predicting ascites existence and distinguishing early stage EOC from advanced stage disease.But serum albumin levels of the patients with ascites have been found lower than the patients without ascites as expected.

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Table 1 Age and tumor type of patients with or without ascites

	With ascites (n=48)	Without ascites (n=32)	p value
Age	51(37-76)	57 (29-76)	NS
Tumor types	n (%100)	n (%100)	
Serous adenocarcinoma	24 (50)	15 (46,87)	NS
Mucinous adenocarcinoma	11(22,91)	8 (25)	NS
Endometrioid adenocarcinoma	11 (22,91)	7 (21,87)	NS
Clear cell carcinoma	2 (4,16)	2 (6,25)	NS

NS; p>0.05

Table 2 Tumor size , albümin and tumor indicators of patients with and without ascites

	With ascites (n=48)	Without ascites (n=32)	p value
Tumor size (cm)	12.5 (5-25)	9.5 (4.0-25)	NS
Albumin (gr/dL)	3.3 (1.2-4.6)	3.7 (2.4-4.7)	0.018
CEA (ng/mL)	2.2 (0.2-77.8)	2 (0.2-1550.1)	NS
AFP (IU/mL)	2 (1-250)	2.1 (1.1-21.8)	NS
Ca 125 (U/mL)	320 (4.1-17884.0)	149(12-4616.8)	NS
Ca 19-9 (U/mL)	7.5 (0.8-861.0)	8.3(0.8-1542)	NS

NS; p>0.05