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Evaluation of Tumor Markers (CEA, CA 15-3, CA 125) in Endometrial Cancer Differentiation and Abnormal Uterine Bleeding

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ABSTRACT

Background & Objective: Endometrial cancer is the most prevalent type of genital system cancers. It is needed to assess discrimination power of CEA, CA 15-3, CA 125 tumor markers in endometrial cancer patients and moreover in cases with abnormal uterine bleeding. We examined tumor markers (CA 15-3, CA 125, CEA) in differentiating endometrial cancer and unusual uterine bleeding.

Materials & Methods: The present case-control study was conducted on 60 women with endometrial cancer and evidence of abnormal uterine bleeding who referred to Ali Ibn Abitaleb Hospital in Zahedan in 2021. The sampling method was easy and accessible and was used to collect observation information, examination, and data form data. For data analysis, SPSS software version 26, statistical graphs and independent t-test were used.

Results: The difference in serum levels of CEA marker tumor in patients of case (endometrial cancer patients) and control (abnormal uterine bleeding patients) was statistically significant. Differences in serum levels of CA 15-3 tumor marker in patients between case group (endometrial cancer patients) and control (patients with abnormal uterine bleeding) and difference in serum levels of CA 125 tumor marker in patients between case (endometrial cancer patients) and control groups (bleeding patients) uterine abnormalities were not statistically significant.

Conclusion: Serum level of CEA tumor marker has a statistically significant relationship with endometrial cancer patients and abnormal bleeding patients, but serum tumor marker level CA 15-3 and serum tumor marker CA 125 and with endometrial cancer patients and abnormal bleeding patients do not have.

Keywords: Abnormal Uterine Bleeding, Endometrial Cancer

Introduction

Endometrial cancer is the common type of the female genital system cancers with age standardized incidence rate of 8.7 per 100000 and death rate of 1.8 per 100000 **(1)**. Despite the high mortality and morbidity, there is no standard method for diagnosis of this cancer. This cancer is symptomatic in the early stages, and 75-90% of endometrial cancer patients experience atypical uterine bleeding in the early stages; therefore, the main attention should be on the correct evaluation at the time of symptoms **(2, 3)**. Several risk factors for the incident of endometrial cancer have been identified. Most of these risk factors are related to the long-term stimulation of estrogen without progesterone on the endometrium **(4)**. In such situation, the endometrium should be checked early and more carefully. Eighty percent of endometrial cancer cases are endometrioid adenocarcinoma (type 1) and 20% are serous carcinoma or clear cell carcinoma (II), which emphasizes the importance of long-term contact with endogenous estrogen or estrogen without progesterone as a trigger for endometrioid adenocarcinoma **(1, 5)**. Obesity, nulliparity, diabetes mellitus and high blood pressure are other determinants of cancer **(6, 7)**. Also, administration of tamoxifen after menopause increases the risk of endometrial cancer **(8)**. There is controversy about the role of phytoestrogens in endometrial cancer, and some studies have even suggested a protective role in phytoestrogens **(9)**.

Endometrial precancerous lesions include endometrial hyperplasia, with a prevalence of 2-10% in premenopausal age and up to 20% after menopause. It can be predicted that up to 10% of postmenopausal women have endometrial hyperplasia without

symptoms. The importance of endometrial hyperplasia is related to the development and transformation into endometrial carcinoma **(10)**. The most common symptom of endometrial neoplasia and hyperplasia is abnormal bleeding; therefore, diagnostic measures are performed for all women at the age of menopause **(11, 12)**. However, considering the costs, discomfort of diagnostic tests, demographic and clinical factors, it is better the screening be applied only for women at risk. Association between female infertility and endometrial cancer has been suggested **(13)**. In premature menarche and late menopause and estrogen-secreting tumors, the probability of infection is higher. BRCA mutation was related to an elevated risk of endometrial cancer **(14)**.

Since tumor spread detection methods such as x-ray, ultrasound and computerized tomography are associated with many limitations, nowadays, there are other methods that are non-invasive, low-cost and fast. One of these methods is the investigation of tumor markers of carcinoembryonic antigen (CEA) and Cancer Antigen 125 (CA-125) **(15, 16)**.

CEA has 200 kilo Daltons molecular weight, which it's very high levels have been proven to be related with metastasis of the cancer and worse prognosis in many tumors in several studies. CA 15-3 is an antigen that is present in the bloodstream along with endometrial cancer and is sensitive and specific in patients with endometrial cancer with metastasis **(15, 16)**. However, the use of this marker has been limited because the level of this marker in the serum of patients with heart failure and liver diseases is also increased. Therefore, the use of this tumor marker along with other common diagnostic methods is being investigated. Therefore, there is a fundamental need for more sensitive and specific tumor markers in addition to CA 125 to diagnose and investigate the treatment process of uterine cancer patients. With considering above issue, the present study aimed to compare CEA, CA 15-3, CA 125 tumor markers in endometrial cancer patients as well as in patients with abnormal uterine bleeding.

Methods

This study was a case control design. The study population includes all women with endometrial cancer or abnormal uterine bleeding, admitted to Ali Ibn Abi Talib hospital, affiliated to Zahedan University of Medical Sciences during 2020-2021. There were 60 women who were divided into two groups: patients with endometrial cancer (n=30) and patients with abnormal uterine bleeding (n=30). Inclusion criteria include age older than 18 years, definitive diagnosis of endometrial cancer based on the results of papilloma pathology, diagnostic curettage or hysterectomy, agreement to contribute in the study. Exclusion criteria were patients who have had endometrial cancer but were treated before sampling which includes surgical and non-surgical treatments, patients who have undergone hormonal treatments, patients with underlying diseases such as tuberculosis, liver, kidney and intestinal diseases, and those with history of chemotherapy and radiotherapy before sampling. Information about age, education, and occupation as well as the exact amount of tumor markers including CA 125, CEA and CA 15-3 were extracted from medical records. The mean (standard deviation) of tumor markers were expressed according to the study groups. The statistical difference of tumor markers according to the study groups was tested using independent t test. The SPSS version 23 (IBM, USA) was used for data analysis at the 0.05 significant levels.

Results

The results of the independent t test are shown in Table 1. The level of three studied tumor markers was higher in cases than in controls. The mean difference of CEA between the two study groups was 13.5 (P <0.001). There was no difference in levels of CA 15-3 and CA 125 between the two study groups, with mean differences of 0.36 (P =0.20) and 0.03 (P =0.92), respectively.

Table 1. The comparison of tumor markers according to cases and controls.

	Case	Control	
Tumor markers	Mean (SD)	Mean (SD)	*p*-value
CEA	14.78 (30.89)	1.28 (0.53)	<0.001
CA 15-3	2.82 (1.44)	2.46 (0.46)	0.20
CA 125	3.52 (1.47)	3.49 (0.91)	0.92

Discussion

The present study aimed to compare the level of tumor markers between endometrial cancer patients or in patients with obvious unusual uterine bleeding. The results showed the level of three tumor markers including CEA, CA 15-3 and CA 125 in patients with endometrial cancer was higher than in patients with abnormal uterine bleeding, however, the difference in level of CEA was statistically significance between the two study groups.

Our study suggests evidence about the difference of CEA in endometrial cancer cases compared to patients with abnormal uterine bleeding. Previous studies indicate the role CEA in monitoring of patients with

endometrial cancer after receiving treatment, so that during radiation therapy the CEA level is increased **(17)**. In one study in India, the authors mentioned that due to the changes in the lifestyle and increasing the rate of obesity, the rate of endometrial cancer in India is growing. Their study was conducted for detection of tumor markers that were in associated with differentiation of endometrial cancer as well as abnormal uterine bleeding. CA 125, CA 15-3, CEA and prolactin levels were elevated in endometrial cancer patients compared to abnormal uterine bleeding patients. In this study, the CA 125 alone with a 52.63% sensitivity and 80% specificity was a better marker for the early diagnosis of endometrial cancer. Serum CA 125 levels as an individual tumor marker can diagnose of endometrial cancer **(18)**. In another study in Iran, the significant association was found between age and CA-125 serum levels and CA-125 levels had a statistically significant relationship with the presence of ovarian cancer. In the former study, sensitivity, and specificity of the CA-125 were 80.1%, and 53.5%, respectively. Moreover, CA-125 had the 48.4% positive predictive value (PPV) and 83% negative predictive value (NPV). They point out that CA-125 is not suitable for screening, but it is valuable for tumor removal **(19)**. It argued that a serum concentration of CA-125 is not accurate enough to diagnose endometrial tumors and prolactin secretion influences the credibility of CA-125 for diagnosis of endometrial cancers at the early stages **(20)**. The diagnostic power of CA 125 is the function of menopause. For example, the combination of CA 125, HE4, and age has highest prognostic power of 89% for with ovarian cancer among premenopausal patients while among postmenopausal patients ROMA had best prognostic value. Sensitivity and specificity of CA 125, HE4, and ROMA also can be modified by menopause status **(6)**.

Several limitations should be considered. First, our study was a case control design; however, longitudinal and prospective studies are needed to evaluate the prognostic value of tumor markers for endometrial cancer. Second, we performed univariate analyses; however, true prognostic value would be estimated in multivariable analyses after adjusting confounders and finally limited sample size resulted in lower power to distinguish the difference of tumor markers between two study groups.

Conclusion

In conclusion, the level of CEA was statistically different between endometrial cancer patients and patients with abnormal uterine bleeding. This marker can be considered for early diagnosis of endometrial cancer and monitoring of treatment among such patients.

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Conflict of Interest

The authors declare no conflict of interest.

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None.

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