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ORIGINAL ARTICLE

Comparison of Adenosine Deaminase (ADA) and Cancer Antigen 125 (CA 125) Levels in Epithelial Ovarian Tumors

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Abstract

Introduction: We aimed to determine serum adenosine deaminase (ADA) and cancer antigen 125 (CA 125) levels in patients with epithelial ovarian tumors.

Methods: A total of 75 patients with 47 malignant and 28 benign epithelial ovarian tumors were included in this case control study. On the morning of the operation, serum CA 125 and ADA levels were determined. Postoperative epithelial ovarian tumor patients were divided into two subgroups as benign and malignant histopathologically. We evaluated whether there was a correlation between tumor levels and serum CA-125 and ADA levels of subgroups and malignant patients.

Results: Of 47 patients with malignant epithelial ovarian cancer, 20 had early stage (stage 1-2) and 27 had advanced stage (stage 3-4) tumors. Serum CA-125 (26.38 vs 44.93, $p<0.001$) and ADA levels (29.91 vs 42. 82, $p\leq0.05$) were significantly higher in malignant epithelial ovarian tumors than in benign epithelial ovarian tumors. There was no significant correlation between ADA levels.

Discussion and Conclusion: This study showed that serum ADA levels in patients with epithelial ovarian cancer can be used as a biomarker in combination with other parameters for predicting malignancy in ovarian cancer. In order to validate these clinical data, large-scale studies of epithelial ovarian tumors are needed.

Keywords: Adenosine deaminase, cancer antigen 125, epithelial ovarian cancer

Ovarian cancer in women constitute 4% of genital cancers and approximately 23% of gynecological cancers. Unlike other gynecologic cancers, more than half of the patients are diagnosed in advanced stage III-IV because ovarian cancer does not have specific signs and symptoms that allow patients to consult a physician [1]. While the 5-year survival rate is 30-55% in advanced ovarian cancer, it is above 80% in early stage ovarian cancer. There are different types of ovarian cancers, but epithelial ovarian cancer (EOC) is the most common type and represents 95% of ovarian cancers [2]. Epithelial ovarian cancer is the most common cause of death from gynecologic neoplasia [3–5]. This high

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mortality rate is due to the insidious course and the lack of effective screening methods [2, 5, 6]. Current methods such as abdominal and transvaginal ultrasonography, color flow doppler, and CA-125 are not specific enough to detect early, curable ovarian cancer by population screening [7].

Cancer antigen 125 (CA 125) is an antigenic determinant of a high molecular weight glycoprotein recognized by a monoclonal antibody (OC 125). It is expressed by the epithelial ovarian cancers and other tissues of Müllerian origin [8]. CA 125 is considered to be one of the reliable markers for ovarian cancer [9]. Ca 125 is a sensitive but non-specific test. Especially in premenopausal women, the diagnostic value is not high. The low specificity is due to the increase in both common benign gynecological conditions and non-gynecological diseases. This reduces the usability of CA 125, especially in the premenopausal period [10].

Adenosine deaminase (ADA) is commonly found in the tissues and body fluids and its most important biological activity is associated with the lymphoid tissue. Because ADA is required for the proliferation, maturation and differentiation lymphocyte [11]. ADA is an enzyme involved in the hydrolytic conversion of adenosine to inosine in the purine salvage pathway. This enzyme is important to prevent accumulation of toxic metabolites in the rapid proliferation of cells [12]. It has been reported that in malignant tissue, ADA activity which shows the increase in DNA synthesis is increased [13]. ADA serum levels increase in patients with ovarian [14], breast and colorectal cancer [15–17]. In inflammatory diseases such as rheumatoid arthritis [18], systemic lupus erythematosus [19, 20], Crohn's disease [21] and ulcerative colitis [22], the relationship between the activation of the disease and ADA level was found. In addition, it is used for diagnosis in tuberculous pleuritis [23].

Studies have shown that adenosine is an anti-inflammatory molecule and acts as an immunosuppressive agent [24]. ADA has an effect of increasing inflammation by breaking down adenosine. ADA activity increases after T lymphocytes respond to antigenic stimulation. Therefore, ADA is accepted as a non-specific marker of cellular immunity by T lymphocyte activation [25]. It is reported that in women with gynecologic malignancies, when the peripheral lymphocyte ADA enzyme is not present or below the control [26], the disease develops faster and serum ADA level is elevated in malignant ovarian tumors [14]. In recent years, potential tumor markers that can be used alone or in combination with CA 125 have been investigated in order to increase the diagnostic specificity of CA 125. In our study; We divided the EOC into two subgroups as benign and malignant histopathologically. We investigated whether serum CA 125 and ADA levels were correlated between the two groups. We also investigated the relationship between the stages of the malignant group and serum markers. To investigate whether serum ADA levels can be used as a biomarker in combination with other parameters in the prediction of ovarian malignancies.

Materials and Methods

This study was performed between January 2011 and January 2013 in the gynecological oncology clinic of Erciyes University Medical Faculty Gevher Nesibe Hospital with preoperative ADA and CA125 levels. A total of 75 patients with epithelial ovarian tumors, 28 benign and 47 malignant, were included in the study. The study was approved by the ethics committee of Acıbadem University. This study was designed retrospectively and data were obtained from hospital records.

The patients who admitted to the clinic for adnexal mass and underwent laparotomy and from those the ones whom preoperative ADA and CA 125 levels were checked were included in the study. Age, menopausal status, tumor stage, invasion sites and lymph node involvement were evaluated. None of the patients included in the study had previously been treated for cancer and the diagnosis of adnexal mass had just been made. The patients previously diagnosed with ovarian or fallopian tube cancer; patients diagnosed with one of the other cancers in the last 5 years or currently receiving chemotherapy for fallopian tube cancer, ovarian cancer, or primary peritoneal carcinomas; those diagnosed with tuberculosis; the patients with inflammatory disease and known systemic disease were not included in the study.

Serum ADA and CA-125 levels were evaluated preoperatively by ELISA. According to histopathological results, the patients were grouped as benign and malignant and the analyses were performed in these subgroups.

Statistical analysis was performed using SPSS 15.0 data analysis method. In the study, the data were evaluated as two-way with 95% confidence interval. In addition to descriptive statistics, Student T test or Mann Whitney U test were used to compare the data. Spearman correlation analysis was used to determine the relationship between serum levels of biological markers and cancer stage and histopathological type. P value ≤ 0.05 was considered as statistically significant.

Results

Laparotomy was performed in 75 patients with pelvic mass. Twenty-eight patients (37.3%) were diagnosed with benign epithelial tumors and 47 patients (62.6%) had malignant disease. 20 of 47 patients with malignant epithelial tumors were early stage (stage 1-2) and 27 of 47 patients were advanced stage (stage 3-4). Figure 1 shows the distribution of malignant cases according to the stages. Table 1 shows the age of patients and the distribution of ADA and CA 125 levels in benign and malignant tumors. Figure 2 shows the comparison of ADA and CA 125 levels in benign and malignant cases. ADA levels were significantly higher in patients with malignant tumors than patients with benign tumors (29.91 vs 42.82, $p \leq 0.05$). CA 125 levels were similarly higher in the malignant group (26.38 vs 44.93, $p<0.001$).

The correlation between biomarkers and tumor behavior (benign or malignant) is summarized in Table 2. There was no significant correlation between serum ADA levels and tumor stage and size in malignant masses ($p>0.05$). There was no correlation between benign masses and CA 125 and ADA levels. However, there was a statistically significant correlation between malignancy and biomarker levels ($p<0.05$).

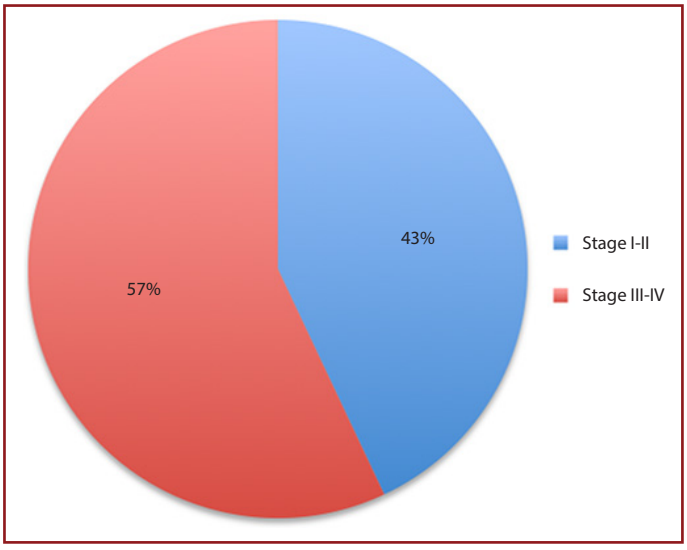

Figure 1. Distribution of malignant epithelial ovarian cancer cases by stage.

Table 1. Comparison of age, ADA and CA 125 levels of patients

	Benign Epitelial Tumor (n=28)	Malignant Epithelial Tumor (n=47)	p
Age	53.7±11.3	55.5±13.2	0.78
ADA	29.91±13.43	42.82±24.49	0.025
CA-125	26.38±18.81	44.93±28.81	0.001

Discussion

EOC is the most common cause of death from gynecological neoplasia, and its 5-year survival rate is 30-55% in advanced stage ovarian cancer, while it is above 80% in early stage ovarian cancer [3–5]. This high mortality rate in ovarian cancer is due to its insidious course and lack of effective screening methods [2, 5, 6]. Current methods such as abdominal and transvaginal ultrasonography, color flow doppler, and CA-125 are not specific enough to detect early and curable ovarian cancer through population screening [7]. Therefore, there is a need for markers that will help to distinguish malignant-benign in adnexal masses. In this study, we aimed to investigate ADA and CA125 levels in adnexal masses.

ADA is an enzyme commonly found in tissues and body fluids [11] and plays a role in the hydrolytic conversion of adenosine to inosine in the purine salvage pathway. This enzyme is important to prevent accumulation of toxic metabolites in the rapid proliferation of cells [12]. It is stated that increased ADA activity plays an important role in the salvage pathway activity of malignant tissues and will provide more nucleotides to maintain DNA synthesis due to the increase in salvage activity in the rapid proliferation of malignant cells [13]. ADA serum levels increase in many cancers such as ovarian [14], breast and colorectal cancer [15–17]. Many studies have shown that ADA increases as a serological tumor marker in rapidly growing malignancies.

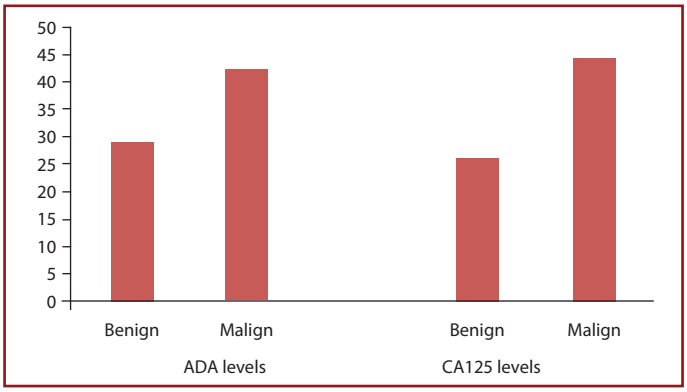

Figure 2. Comparison of ADA and CA125 levels in benign and malignant epithelial ovarian tumors (ADA U/L, CA125 U/mL).

Table 2. Correlation between ADA, CA-125 levels and histopathological results

Biomarkers	Benign Epitelial Ovarian Tumors	p	Malignant Epitelial Ovarian Tumors	p
ADA	0.230	0.25	0.67	0.03
CA-125	0.11	0.48	0.420	0.001

On the other hand; slow-growing, well-differentiated tumors are reported to express no significant ADA activity [26]. Specchia G et al. [27] studied ADA activity in 31 patients with gynecologic malignancies, 19 of which were portio carcinoma, 7 of which were endometrial adenocarcinoma, 3 of which were ovarian cancer, 1 of which was cervical adenocarcinoma and 1 of which was liposarcoma with myxoid. They observed that the disease develops more rapidly when the enzyme is absent or well below the controls. It has been suggested that low lymphocyte ADA in tumor tissue is a more sensitive indicator of suppressed cellular immunity and has been proposed as a compensatory mechanism against rapid purine and DNA metabolism in cancer cells [28]. In 2005, Pragathi, P. et al. [12], including 50 patients with ovarian cancer (serous and mucinous), 28 with benign ovarian tumor (cystadenoma) and 20 healthy women in the control group; compared serum ADA, CA-125 and 5'-nucleotidase (5'-NT) activities; ADA levels in the ovarian cancer group were significantly higher than in the control group and significantly higher than in the benign ovarian tumor group. They stated that high 5'-NT and ADA levels are strictly related to the presence of cancer cells. Urunsak IF et al. [14], in their study which to investigate serum and peritoneal fluid ADA activity in benign and malignant ovarian tumors; found that serum and peritoneal fluid ADA levels were significantly higher in ovarian cancer than benign ovarian tumors (p=0.001). In our study, the mean serum ADA level in the benign EOC group was 29.91 U/L and the mean serum ADA level in the malignant EOC group was 42.82 U/L. When malignant EOC group and benign EOC group were compared; the increase in serum ADA levels in patients with malignant EOC was significant, similar to the results of Pragathi, P. et al., and this increase was statistically significant in parallel with the results of Urunsak IF et al.

CA 125 is a sensitive but nonspecific test when ovarian cancer is used alone [29]. The low specificity is due to the increase in common benign gynecological conditions and non-gynecological diseases. This reduces the usability of CA 125, especially in the premenopausal period [10]. Chhunthang Thanpari et al. [30] evaluated CA-125, ADA and other biochemical parameters in 43 premenopausal and 21 postmenopausal ovarian cancer patients; found that serum CA 125 and ADA levels were significantly higher in both premenepausal and postmenepausal ovarian cancer patients than in the control group. Pragathi, P. et al. [12] reported that the threshold for ADA was 30 U/L, which is the upper limit of the range obtained for healthy controls. The sensitivity of ADA as a tumor marker was 56% and the specificity was 78%. They also indicated that there was no significant correlation between CA 125 and ADA and CA 125 with 5'-NT. They stated that high levels of 5'-NT and ADA depend on the presence of cancer cells and therefore these two parameters may be useful in differentiating ovarian cancer from benign tumors of ovarian cancer, in addition to the well-known marker of ovarian cancer CA-125.

CA 125 plasma level increases in 50% of stage I ovarian cancers and in 90% of stage II-IV ovarian cancers [32]. Urunsak IF et al. [14] stated that serum ADA levels differ significantly according to histopathological subtypes and grades of ovarian cancers, but there is no significant difference between benign and low-grade malignant tumors in terms of serum ADA levels. In our study; Ovarian cancers were divided into two subgroups as benign and malignant histopathologically and serum levels of both ADA and CA 125 were found to be significantly higher in patients with malignant tumors than patients with benign tumors. Although increased ADA levels, especially in the presence of metastasis, may be due to different sources other than tumor [16]; in our study, no significant correlation was found between serum ADA levels and tumor stage and tumor size.

Ovarian masses are common pathologies in gynecology practice. Therefore, malignant-benign distinction in ovarian masses is important in terms of good distinction between patients to be included in the follow-up protocol and those requiring surgical treatment, and to reduce unwanted surgical interventions and associated morbidity and mortality [31]. Elevation of CA 125 in common benign gynecological conditions and non-gynecological diseases decreases its usability especially in premenopausal period [10]. In addition, low positive CA 125 in stage I suggests that it is insufficient for the early diagnosis of ovarian cancer [8, 32]. To date, in low number of studies to determine the prognostic value of serum ADA levels in ovarian cancer; elevated serum ADA levels were described in patients with ovarian cancer [12, 14]; in fact, this increase is reported to be in both premenepausal and postmeneposal ovarian cancer patients [30].

As a result; CA 125 and ADA levels increase in malignant ovarian tumors. The results of this study suggest that serum ADA levels can be used as a biomarker in combination with other parameters in the prediction of ovarian malignancies. However, further studies are needed to determine the role and prognostic value of ADA in the development of ovarian cancer.

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Conflict of Interest: None declared.

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