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Serum ischemia modified albumin and endometrial cancer: a prospective case-control study

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Summary

Objective: To investigate the importance of ischemia modified albumin (IMA) in the diagnosis and evaluation of endometrial carcinoma. *Material and Methods:* Serum IMA levels of patients with and without endometrial cancer were measured by the calorimetric assay technique and their absorbance units were compared. *Results:* A total of 128 women were included in the study; 64 of these women were endometrial cancer patients and 64 of them were in the control group. The median age for these groups were 58.5 and 56 years, respectively. There was no significant difference in terms of age, body mass index, and serum albumin levels between the groups ($p > 0.05$). In the endometrial cancer group, the median serum IMA level was 0.489 (0.401-0.611), while in the control group the median serum IMA level was 0.490 (0.407-0.589). There was no significant difference between these two groups ($p = 0.467$). In the type 1 endometrial cancer group, the median serum IMA level was 0.452 (0.401-0.590), while in the type 2 endometrial cancer group the median serum IMA level was 0.559 (0.462-0.611) A significant difference was found between types 1 and 2 endometrial cancers ($p < 0.001$). *Conclusions:* The IMA level does not appear to be an additional predictive marker of preoperative diagnosis and evaluation of endometrioid type endometrial cancer when compared to the healthy control group; on the other hand, IMA may be a marker for the detection of type 2 endometrium cancers when compared with type 1 endometrium tumors. However, further randomized controlled trials are required to make a comparison between type1 and type2 endometrial cancers.

Key words: Endometrial cancer; Endometrioid histopathology; Ischemia modified albumin (IMA).

Introduction

Endometrial cancer is the most common gynaecological cancer [1]. It appears often with postmenopausal bleeding and irregular bleeding patterns during the premenopausal period, however, it can also be recognized by ultrasonography if it is asymptomatic [2].

Endometrial cancer can be divided into two distinct types in relation to histology, risk factors, and prognosis. Type 1 endometrial cancer constitutes 80–90% of all endometrial cancers. It is mainly diagnosed in relatively young women and the prognosis is better [3]. Type 1 endometrial cancer is estrogen dependent, of endometrioid histology, and strongly linked to obesity [3, 4]. Type 2 endometrial cancer is known to be less hormone dependent and non-endometrioid. It is comprised of higher grade histology (papillary serous carcinomas and clear-cell carcinomas, etc.) [5, 6]. Type 2 tumors have a higher rate of recurrence and more often metastasis is present with a higher grade of diagnosis when compared to type 1 tumors [7]. Endometrioid type is the most frequently encountered histological type of endometrial cancer, and the five-year survival rate in early stages is 81-91% [8]. In non-endometrioid and advanced cancers, this rate drops to 10-40% [6, 9].

Although it is common today, there is neither an effective screening method nor a standard non-invasive serum marker used in the diagnosis of endometrium cancer [10]. Nowadays, the requirement for tumour markers that can reveal both early diagnosis and screening as well as post-surgical recurrence has become important. Thus far, biological and genetic markers such as Ca-125, Ca-15-3, CEA, VEGF, HE4, YKL-40, and DKK-3 have been studied in the diagnosis of endometrial cancer [11, 12].

The N-terminal portion of the albumin molecule, known as the amino group, is the site of attachment of metal ions such as Co^{+2} (cobalt), Ni^{+2} (nickel), and Cu^{+2} (copper) [13] [14]. In the case of ischemia, hypoxia or acidosis, the binding capacity of these metals to the N-terminal end of albumin is reduced due to free oxygen radical damage and the resulting modified form of albumin is called ischemia modified albumin (IMA) [15, 16].

In 2003, IMA was approved by the Food and Drug Ad-

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ministration (FDA) for use in diagnosing acute coronary syndromes [17]. The present data suggest that IMA is not only present in cardiac ischemia but also in some cancers (bladder, stomach, colorectal cancers, etc.)[18-20], diabetes [21], polycystic ovary syndrome [22], some perinatological problems [23], sepsis, acute appendicitis, and rheumatoid arthritis [24-26].

The aim of this study was to investigate the importance of serum IMA in the diagnosis and/or evaluation of endometrial cancer.

Materials and Methods

The present study included patients with endometrial cancer (endometrioid and non-endometrioid type) who were diagnosed and healthy women as a control group who were admitted to this clinic between 2015 and 2016. The study protocol was approved by the Local Institutional Ethical Committee. All patients signed an informed consent that allows this institution to use their clinical data.

The study population included women who were diagnosed in the pathology department with endometrial cancer. Patients with chronic diseases (diabetes, asthma, chronic renal failure, etc.), serum albumin levels below 2.5 gr/dl or above 5 gr/dl, synchronous malignancies, under medication therapy (theophylline, nitrate, anticholinergic, calcium channel blockers, etc.), and patients with incomplete medical records were excluded from the study. The control group's patients were selected from healthy women who applied to the out-patient clinic for a routine control. They were aged between 40 and 78 years.

Tumor characteristics were abstracted from original pathology reports, and the following data were recorded: primary tumor size (< 2 cm or ≥ 2 cm), depth of myometrial invasion (MMI) (< 50% or ≥ 50%), grade, presence of lymphovascular space invasion (LVSI,) stage, and histological subtype. All surgical specimens were examined and interpreted by gynecology pathologists. Architectural grading was defined by standard International Federation of Gynecology and Obstetrics (FIGO) criteria. All tumors were staged according to the FIGO staging system.

Demographic features (age, body mass index) and serum albumin were evaluated and compared between endometrial cancer and control groups. Then, serum IMA levels of patients with and without endometrial cancer were measured by the calorimetric assay technique and their absorbance units were compared.

The IMA levels were evaluated and compared according to pathological findings (MMI, tumour size, grade, LVSI), stage, and histological subtype in endometrial cancer group. IMA concentrations were analyzed by measuring the complex, composed of dithiothreitol and cobalt that is unbound to albumin by employing the colorimetric method in a spectrophotometer. The analyses in the spectrophotometer were performed at 470 nm for the detection of absorbance of the specimens, and the results were given as absorbance units (ABSU). Intra-assay and inter-assay coefficients of variability for the IMA assays are 3.5% and 6.1%, respectively.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 23). The data was expressed as median and range for continuous variables and binary variables were reported as counts and percentages. The significance of differences between groups was determined by using the independent *t*-test for normal distributions, and by using the Mann-Whitney U test for abnormal distributions. The *p*-values less than 0.05 were accepted as the significance level.

Table 1. — *Characteristics of all patients.*

	Cases (n=64)	Control (n=64)	*p* value
Age, y, median	58.5 (42-78)	56 (46-69)	0.130
BMI (kg/m^2)	31.2 (19.5-46.4)	30.1 (20.8-44.4)	0.572
Albumin (gr/dl)	4 (2.8-4.8)	3.9 (2.9-4.8)	0.593
IMA (ABSU)	0.489 (0.401-0.611)	0.490 (0.407-0.589)	0.467

IMA: ischemic modified albumin, ABSU: absorption unit, BMI: body mass index

Table 2. — *Comparison of pathologic findings with regards to IMA results.*

	Cases	IMA value (ABSU) (median, range)	*p* value
Myometrial invasion			
< 1/2	44 (68.8%)	0.487 (0.401-0.591)	0.896
≥ 1/2	20 (31.3%)	0.510 (0.411-0.611)	
Tumor size			
< 2 cm	23 (35.9%)	0.487 (0.401-0.611)	0.944
≥ 2 cm	41 (64.1%)	0.490 (0.411-0.585)	
Grade			
1	40 (62.5%)	0.480 (0.411-0.590)	0.165
2 or 3	24 (37.5%)	0.522 (0.401-0.611)	
LVSI			
Absent	44 (68.8%)	0.487 (0.401-0.590)	0.519
Present	20 (31.3%)	0.501 (0.414-0.611)	
Stage			
I-II	51 (79.7%)	0.488 (0.411-0.604)	0.894
III-IV	13 (20.3%)	0.491 (0.401-0.611)	
Histologic type			
1	48 (75 %)	0.452 (0.401-0.590)	<0.001
2	16 (25 %)	0.559 (0.462-0.611)	

IMA: ischemic modified albumin, LVSI: lymphovascular space invasion, ABSU: absorption unit

Results

The current study included 64 patients with endometrial cancer [48 with endometrioid type and 16 with non-endometrioid type (11 serous, 2 clear cell, 3 mixed)] and 64 healthy women. The median age was 58.5 (range, 42-78) years in the endometrial cancer group while the median age was 56 (range, 46-69) years in the control group. Body mass index was calculated as 31.2 (range, 19.5-46.4) kg/m^2 in the endometrial cancer group and 30.1 (range, 20.8-44.4) kg/m^2 in the control group. The median albumin level was 4 (range, 2.8-4.8) gr/dl in the patient group and 3.9 (range, 2.9-4.8) gr/dl in the control group.

IMA levels were calculated as 0.489 (range, 0.401-0.611) ABSU in the endometrial cancer group and 0.490 (range, 0.407-0.589) ABSU in the control group (Table 1). There was no significant difference in age, body mass index, serum albumin levels, and IMA levels between the two groups ($p > 0.05$) (Table 1).

In the endometrial cancer group, 20 (31.3%) patients had ≥ 50% myometrial invasion. Forty-one (64.1%) patients had a tumour size of ≥ 2 cm. 40 (62.5%) patients had grade 1 tumour, and 24 (37.5%) had grade 2 or 3 tumours. Twenty (31.3%) patients had LVSI. Fifty-one (79.7%) patients

Table 3. — *Studies analysing relationship between IMA and cancer in the literature.*

Study	Disease	Cases (n/mean IMA value)	Control (n/mean IMA value)	*p*-value
Stachowicz-Stencel *et al.*	Soft tissue sarcoma	47 / 119.8 ± 27.5 U/ml	30 / 87.3 ± 38.3 U/ml	0.006
2011 [33]	Neuroblastoma	52 / 114.6 ± 36.6U/ml	30 / 87.3 ± 38.3 U/ml	0.016
Fidan *et al.* 2012 [19]	Gastric cancer	42 / 0.405 ± 0.111 ABSU	35 / 0.271 ± 0.066	0.001
Ellidağ *et al.* 2013 [20, 32]	Bladder cancer	40 / 0.588 ± 0.07 ABSU	40 / 0.474 ± 0.04 ABSU	< 0.001
	Colorectal cancer	40 / 0.569 ± 0.06 ABSU	39 / 0.469 ± 0.04 ABSU	< 0.001
Present study	Endometrium cancer	56 / 0.667 (0.313-0.883)	64 / 0.639 (0.178-0.932)	0.433

IMA: ischemic modified albumin; ABSU: absorption unit.

were Stage I-II, while 13 (20.3%) patients were Stage III-IV (Table 2).

The pathologic findings and stage of the patients in the endometrial cancer group were compared in terms of IMA values. The number of cases and the median IMA values are shown in Table 2. There was no significant difference in myometrial invasion, tumour size, grade, LVSI, and stage IMA values ($p > 0.05$). When the histological subtypes (type 1 *vs.* type 2) were compared according to the IMA level, there was a significant difference found between these two groups ($p < 0.001$) (Table 2).

Discussion

IMA is an FDA-approved marker for use primarily in ischemic heart disease [17]. It is also a marker used in proinflammatory and inflammatory conditions [26, 27]. The main purpose of this study was to demonstrate the potential of serum IMA as a diagnostic marker in endometrium cancer, as IMA is an indicator of ischemia and inflammation.

A prospective or retrospective study that examines the relationship between gynaecological tumours and IMA is not available in the literature. In this study, no statistically significant difference was found in terms of serum IMA levels between the patients with endometrial cancer diagnosis and the healthy control group, which had similar demographic characteristics (Table 1). Similarly, in the endometrial cancer group, the patients' stage and pathological findings were compared in terms of IMA values with myometrial invasion, tumour size, grade, LVSI, and stage. The obtained IMA results were not found to be statistically significant when compared. However, when comparison was made between type 1 and type 2 endometrial cancers the authors saw that there was a significant difference ($p < 0.001$). They are aware that type 2 endometrial cancers have a different genetic and histopathologic background, and they are responsible for most of the deaths related to endometrial cancers. The present findings can lead studies focusing on the importance of IMA as a prognostic factor for these types of tumours.

The present study included a limited number of patients in this aspect as it is the first prospective study in the literature. Despite the aforementioned limitation, this study provided additional information to the body of knowledge on this topic.

In recent years, different studies have been conducted describing the relationship between inflammation and cancer [28]. This relationship may be due to inflammatory conditions that may directly cause cancer; it may also arise as a consequence of genetic changes that induce inflammation by inducing oncogenesis [29]. Currently, hypoxia and inflammation pathways are reported to be important in the pathogenesis of endometrial cancer and response to treatment [28-30].

Although endometrium cancer is widespread, there is no routine screening system today. A large number of serum markers such as Ca-125, HE4, CEA, Ca15-3, Ca19-9, Ca72-4, Ykl-40, and DKK-3 are studied in the clinical management of endometrium cancer, whereas one of these are accepted as standards [11, 12, 31].

There are a limited number of studies on the relationship between serum IMA levels and cancer in the literature. As there are no studies focusing on the relationship between gynaecological cancers and IMA, the present authors believe that it would be useful to discuss prominent studies that are made on non-gynaecological cancers.

In a prospective study involving 40 colorectal cancer cases, Ellidag *et al.* [32] found that serum IMA levels were statistically important. In another study of the same group, IMA levels of 40 patients with bladder tumours were investigated and they were found to be significantly elevated [20]. Fidan *et al.* [19] found statistically higher serum IMA levels in a case-control study involving 52 gastric cancer cases. Stachowicz-Stencel *et al.* [33] found an increase in serum IMA levels in a prospective study involving 99 paediatric cases of soft tissue sarcoma and neuroblastoma. Da Silveria *et al.* [34] reported that the increase in serum IMA levels in prostate cancer cases was not significant. Radomir *et al.* [18] reported that the difference between preoperative and postoperative IMA levels in colorectal cancer cases was a valuable marker for predicting the complications. Satoh *et al.* [35] also reported that the IMA level in the preoperative phase of colorectal cancer patients showed the failure rate of the surgeon. The studies in the literature on IMA and cancer relation are summarized in Table 3 [19, 20, 32, 33].

Conclusion

The IMA level does not appear to be an additional predictive marker of preoperative diagnosis and evaluation of endometrioid type endometrial cancer when compared with health control group. On the other hand, IMA may be a marker for the detection of type 2 endometrium cancers when compared with type 1 endometrium tumors. However randomized controlled trials are required to make a comparison between type 1 and type 2 endometrial cancers.

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