ORIGINAL RESEARCH PAPER

Volume-7 | Issue-9 | September-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

THE ASSOCIATION BETWEEN MICROSATELLIT INSTABILITY AND THE PROGNOSTIC PARAMETERS IN ENDOMETRIOID TYPE ENDOMETRIAL CARCINOMA

Medicine

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ABSTRACT

Endometrial carcinoma is the most common malignancy of the female genital tract. Endometrioid type is the most common (80%) histotype of it. The prognosis of Endometrioid Endometrial carcinoma greatly depends on the histological grade, stage of the disease and worsens after recurrence. However it's difficult to predict the recurrence risk of it at the beginning of the disease. In our study we researched the relation between Microsatellit Instability and the prognostic factors of Endometrioid carcinoma in order to find out a new predictive marker; but could not find any association. So we considered MSI is not a good prognostic marker in Endometrioid Endometrial Carcinomas.

KEYWORDS

Endometrium, Endometrioid carcinoma, Microsatellit Instability

INTRODUCTİON

Endometrial carcinoma(EC) is the most common malignancy of the female genital tract[1]. Endometrioid type according to World Health Organization is the most common (80%) histotype of EC[2,3]. Endometrioid type Endometrial carcinoma (EEC) is estrogen related and is commonly seen in perimenopausal woman rising in a background of endometrial hyperplasia (Endometrial intraepithelial neoplasia). The average age in EEC is 60 and is the most common malignancy in postmenopausal women. Although most patients with early stage disease have good prognosis, some of them recur early unexpectedly. The prognosis greatly depends on the grade and stage of the disease and worsens after recurrence. Also the prognosis of the patients with advanced disease at presentation or incurable disease by surgery or radiotheraphy are the poorest[4-6]. Because of the variable prognosis of EEC, many studies have aimed to find out new prognostic markers in order to foresee the risk of recurrence at the time of initial diagnosis[1,7].

EECs frequently have molecular alterations which have been searched in some studies in order to find out the prognostic relations. Microsatellite instability(MSI) is the most common molecular alteration seen in EECs. MSI is thought to result from the accumulation of mutations during DNA replication and is thought to be related with inactivating mutations in Mismatch Repair(MMR) genes[8,9]. Loss of DNA MMR leads to an increase in frameshift mutations producing genomic instability at repeat sequences in DNA, emerge as MSI. This genetic alteration potentially affects many cancer related genes[10-12]. Colorectal tumors excibiting MSI are associated with better prognosis and good response to chemotherapy[13-14]. Prognostic and predictive roles of defect in MMR genes have been searched in ECs[15-18] . MSI occurs in about 9-64% of endometrial tumors, the majority of which are sporadic but not hereditary (Lynch Syndrome)[1,3,4,18].

There are four MMR genes clinically studied to find out the MSI: MLH1, MSH2, PMS2 and MSH6[9]. The aim of this study was to assess the MSI status of EECs immunohistochemically and to expose its relation with the prognostic parameters.

METHODS

We analized 82 female patients retrospectively who was histopathologically diagnosed as EEC with the endometrial biopsy at Muğla Sıtkı Koçman University, Faculty of Medicine, Department of Pathology between the beginning of 2013 to the end of -July2018 and later underwent histerectomy with bilateral pelvic lymph node dissection in this study. Clinical parameters of the patients were obtained from the hospital automation system. The hematoxylin-eosin slides of these patients were reviewed by two pathologists (OIC and LT) and representative sections and paraffin blocks of each tumor appropriate for immunohistochemistry were selected. The parameters evaluated were age, tumor grade, depth of myometrial invasion, lymph-vascular space invasion(LVI) and pelvic lymph node metastasis(PLNM). MLH1, MSH2, PMS2 and MSH6 antibodies were applied to the four micrometer thick sections of formaldehyde fixed paraffin embedded tumor blocks by Leica Bond-Max brand fully automatic immunohistochemistry device. For each slide, hematoxylin was used as the counterstain. The antibodies used were as follows: MLH1 (Leica, ES05, 1;50), MSH2 (Leica, 25D12), PMS2 (Leica MOR4G, 1;100), and MSH6 (Leica, PU29, 1;100). Immunohistochemical staining was evaluated with the light microscope (Olympus, BX46 Clinical Microscope- Japan) by the same pathologists. The staining of residual normal endometrium, endometrial stromal cells, endothelial cells and lymphocytes were used as internal positive controls[1,18]. The presence or absence of nuclear staining was evaluated for the immunohistochemical staining of 4 antibodies. MLH1, MSH2, PMS2 and MSH6 protein expressions were considered lost when none of the tumor cell nuclei were stained positive in the presence of an internal positive control[19].

The Kolmogorov-Smirnov test and Q-Q Plot were used to verify the normality of the distribution of continuous variables. Descriptive statistics and categorical variables were given as frequencies (percentages). The Chi-square/Fisher's exact tests were used for categorical variables. Analyses were performed with SPSS Statistics for Windows, Version 20 and two-tailed p-value less than and equal to 0.05 was considered statistically significant.

This Project was evaluated by Muğla Sıtkı Koçman University Research and Publication Ethics Committee with 180096 registration number and 97/2018 desicion number and it was approved in terms of scientific researches and patient ethics.

RESULTS

The mean age of 82 patients included in the study was 58.5 (min 36-max 85). Most of the patients were postmenopausal (n:70, 85.4%), only 12 patients were (14.6%) premenopausal. The parameters evaluated are summarized in Table.

Table: The distribution and the results of the parameters evaluated in the study. (p-value ≤0.05 was considered statistically significant)

Parameter		n	%	MLH1 staining		MSH2 staining		PMS2 staining		MSH6 staining	
				absent	present	absent	present	absent	present	absent	present
Age	<50	12	14.6	3	9	4	8	9	3	5	7
	≥50	70	85.4	32	38	24	46	42	28	33	37
	Total	82	100.0	p=0.220		p=1.000		p=0.325		P=0.765	
Histological tumor grade	Grade 1	29	35.4	13	16	9	20	18	11	11	18
	Grade 2	27	32.9	12	15	11	16	16	11	12	15
	Grade 3	26	31.7	10	16	8	18	17	9	15	11
	Total	82	100	p=0.870		p=0.677		p=0.900		p=0.331	

Depth of myometrial invasion	Absent	21	25.6	7	14	6	15	12	9	8	13
	<50%	29	35.4	16	13	12	17	18	11	13	16
	≥50%	32	39.0	12	20	10	22	21	11	17	15
	Total	82	100.0	p=0.229		p=0.581		p=0.824		p=0.551	
Lymph-vascular space invasion	Absent	57	69.5	25	32	17	40	32	25	22	35
	Present	25	30.5	10	15	11	14	19	6	16	9
	Total	82	100.0	p=0.812		p=0.312		p=0.137		p=0.053	
Pelvic lymph node metastasis	Absent	62	75.6	27	35	18	44	36	26	25	37
	Present	20	24.4	8	12	10	10	15	5	13	7
	Total	82	100.0	p=1.000		p=0.107		p=0.197		p=0.072	

In the uterus all the structures including normal endometrium, stromal cells, lymphocytes, endothelial cells are Microsatellit Stabil normally like the other tissues. MMR genes; MLH1, MSH2, PMS2 and MSH6 repair the mutations. So these antibodies are normally expressed in these cells. Whenever these MMR genes are inactivated, they are no more expressed immunohistochemically (staining:absent) and these cells are named as Microsatellit Instabil(MMR-deficient) anymore[1,3,4,9,18]. So in the table the antibody staining-absent columns represent Microsatellit Instability(MMR-deficiency). We compared the Microsatellit Instability with the age, grade, myometrial invasion and LVI and PLNM. However none of the result were statistically significant as seen in the table. Only the relation of MSH6 with the LVI and PLNM was close to the statistical significance (p=0.053 and p=0.072). The MMR-deficiency of the genes MLH1, MSH2, PMS2 and MSH6 were 42.7%-34.1%-62.2% and 46.3% respectively.

DISCUSSION

In EECs age, histological grade, stage, depth of myometrial invasion, LVI are the most important predictors of lymph-node metastasis and the survival[2]. However some of the tumors(15-20%) with good prognostic factors recur unexpectedly[1,7]. So need for research of new, additional prognostic markers arises in order to predict the risk ratio of recurrence at the time of initial diagnosis. As MSI is the most common molecular alteration seen in EECs(between 9% and 64%), the prognostic value of it has been searched recently; however the results of the studies show that this value is controversial[1,4,18].

In our study, we could not find any statistically significant association between MSI and the classic prognostic parameters in EECs in accordance with the literature. Ruiz et al., Mackay et al. and Zighelboim et al. had reported that MSI had no relation with the prognosis[1,4,16]. These results are in paralel with ours. However in some other studies like performed by Black et al. and Ju et al. it was claimed that the presence of MSI was associated with more favorable clinical outcome[15,18]. On the other hand An et al., found relation between the presence of MSI and worse prognosis[17].

When the previous studies in the literature and the results of our study are regarded; MSI; detected by immunohistochemical staining of MMR genes; MLH1, MSH2, PMS2 and MSH6, was not considered to be a good prognostic marker in Endometrioid Endometrial Carcinomas.

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