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ORIGINAL ARTICLE

Histological and Immunohistochemical Variability in Microsatellite Instability-Associated Endometrial Carcinoma

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ABSTRACT:

Background: Endometrial cancer is the most common gynecological cancer in women. Endometrial cancer is a prevalent gynecological malignancy in women, accounting for roughly 2% of cancer-related fatalities globally.

Objective: To examine the prevalence of microsatellite instability (MSI) in endometrial cancer within our community and its correlation with clinicopathological characteristics.

Patients and method: A cross-sectional study in which all patients who previously diagnosed with primary endometrial carcinomas and underwent for surgical resection during the period of the study were included, Patients with history of pre-operative chemotherapy or radiation therapy were excluded from the study. We review the patient's medical reports, and they were contacted to disclose their personal and familial cancer histories indicative of hereditary cancer predisposition.

Results: No significant differences between appearance of MSI markers across each of tumor stage, FIGO stage, FIGO grade, cervical invasion, adnexal involvement lympho-vascular invasion, and recurrenc, ($P>0.05$), while significant difference were observed across nodal stage and family history, ($P<0.05$).

Conclusion: A significant prevalence of endometrioid tumors in our investigation had aberrant levels of MSI markers, predominantly indicating diminished MLH1/PMS2, and were not linked to hereditary cancer predisposition. A minority of cases exhibited a complete loss of all MSI indicators or an absence of MSH2/MSH6, which was substantially correlated with a family or individual history of malignancy.

Keywords: Microsatellite instability, Endometrial malignancies, Histopathological study.

Conflict of interest: none, declared by authors

Ethical considerations: approved by the authors

INTRODUCTION:

Endometrial cancer (EC) is defined as a malignant epithelial tumor that originates in the endometrium. Most endometrial carcinomas are adenocarcinomas and the most common type is endometrioid adenocarcinoma. EC is the most common malignant gynecological tumor in many countries. Its highest incidence rates are found in the USA and Canada, ranking below breast, bowel and lung cancer [1,2]. From a general perspective, EC is more common in older, white, well-off, obese, and low-parity women [2]. From a specific epidemiological perspective, it is first necessary to make some clarifications about the tumor heterogeneity associated with CE, since this could affect the epidemiological associations. In this regard, the EC is heterogeneous from a histopathological point of view. Although they are often included within the broad category of cancers of the uterine body, sarcomas originating in the endometrial stroma or in the smooth muscle of the uterus should not be considered in this category [3].

As practically all cancers of the uterine body are adenocarcinomas, the EC taxonomy mainly refers to their classification. Thus, reference is made to the endometrioid EC or type I, which represents almost 80% of cases, and type II, which includes adenosquamous carcinomas, adenoacanthoma, capillary serous, mucinous, clear-8 cell, squamous cell, mixed and undefined carcinoma. In this sense, most of the epidemiological studies on EC refer to type I [4,5].

The geographical distribution varies across countries, in USA, EC is the most common gynecological cancer, with 40,100 new cases and 7470 deaths in 2008 [6]. The highest prevalence rates of EC occur in industrialized countries and Northern Europe, while the lowest correspond to third world nations [7].

In Iraq the EC was the 2nd gynecological cancer after the ovarian cancer and its prevalence was varying from 4.21% to 25.59% from all gynecological cancer according to the region in the country [8,9]. The incidence of EC increases sharply during the perimenopausal years, reaching its peak after menopause. The incidence rates decline after the age of 70. The overall rate of EC is estimated to be 33% higher for women who did not undergo hysterectomy or hysterectomy and oophorectomy procedures, although this depends on age [10].

Regarding the pathological features, endocervical carcinoma can manifest as either broad-based polypoid masses or as a diffuse infiltrative development into the myometrium. Extensive

myometrial invasion is typically correlated with a clinically observable enlargement of the uterus [11-13]. However, there are exceptions; sometimes deep myometrial extension is accompanied by a normal-sized uterus, and the growth pattern is like that of a cervical adenoma. This pattern has also been described as "minimal invasive deviation" [14].

The Microsatellite instability (MSI) results from alterations in one or more DNA mismatch repair genes (MLH1, MSH2, PMS2, and MSH6)., leading to dysfunction of the proteins that repair replication errors and triggering the tumor phenotype. These alterations in repair genes can occur through germline mutations in hereditary cases (Lynch syndrome). or through hypermethylation of the MLH1 gene promoter in sporadic cases. The B-RAF V600E gene mutation is associated with inactivation by hypermethylation, but not with germline mutations [15,16].

Approximately 30% of endometrioid endometrial carcinomas exhibit MSI-H, which is absent in other types of endometrial carcinomas. Therefore, its detection is useful in the differential diagnosis of these tumors. Furthermore, the detection of MSI-H, in the absence of the B-RAF V600E mutation, allows for the screening of patients with Lynch syndrome [17,18].

METHODS:

A cross-sectional study in which all patients who previously diagnosed with primary endometrial carcinomas and underwent for surgical resection during the period of the study were included, Patients with history of pre-operative chemotherapy or radiation therapy were excluded from the study. We review the patient's medical reports, and they were contacted to disclose their personal and familial cancer histories indicative of hereditary cancer predisposition. The study included 63 cases who had proved diagnosed primary EC confirmed by biopsy. All of them underwent surgical resections between October 2024 and November 2025 at Baghdad Teaching Hospital. Patients who received pre-operative radiotherapy and /or chemotherapy and those with non-endometrioid histology were excluded from the study.

The medical reports of the all cases were examined, and all patients were contacted to disclose their personal and familial cancer histories indicative of hereditary cancer predisposition, and the slides of all specimens were obtained and examined many times, (**Figures 1 &2**)

Data management and statistical processing were performed using the statistical package for social sciences (SPSS) version 28. Descriptive statistics were presented as frequency (count) and

percentage for categorical variables. Comparative statistic was performed using chi-square test. Fisher's exact test used when chi-square was inapplicable. Level of significance, P. value≤ 0.05 considered significant.

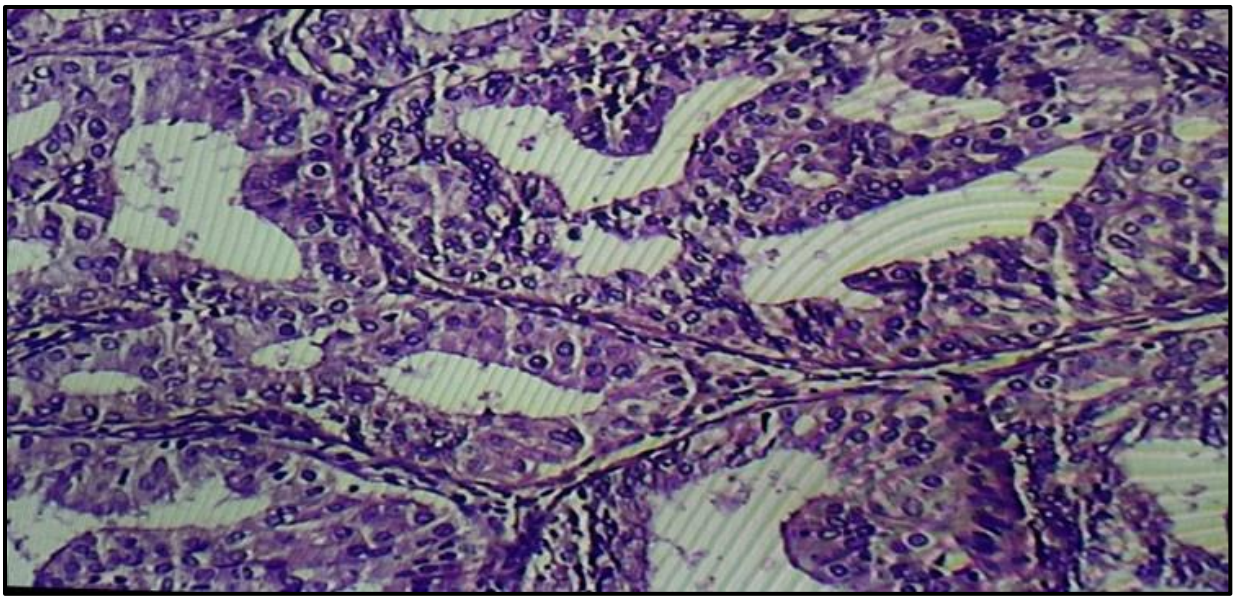

Figure 1. Endometrial cancer

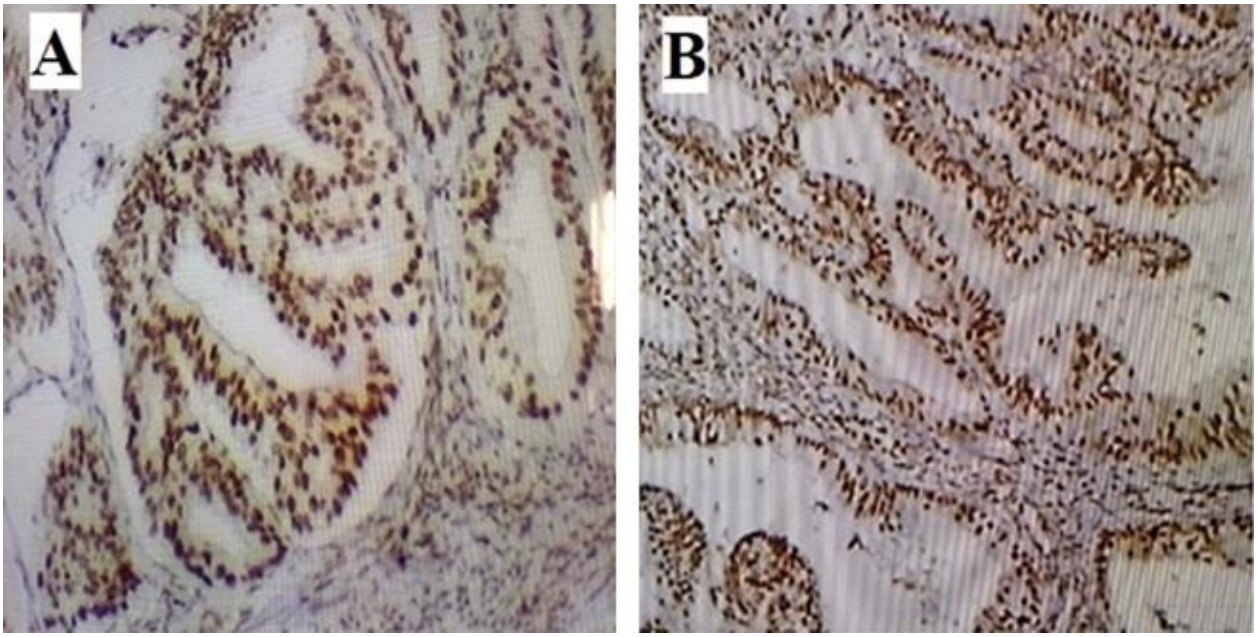

Figure 2. A. MSH2+, B. MIH1+

RESULTS:

Among the studied group, unaltered expression of all markers found in 35 cases (55.6%), Loss of expression in 8 (12.7%) MLH1/PMS2 loss of expression in 17 (27%%), MSH2/MSH6 loss of expression in 2 (3.2%) and isolated MLH1 loss of expression in only 1 case (1.6%). Findings revealed no significant differences between appearance of MSI markers across each of tumor stage, FIGO stage and FIGO grade, (P>0.05), while a significant difference was observed across nodal stage, (P<0.05). Comparison of MSI Markers expression among cases who had cervical invasion, adnexal involvement lympho-vascular invasion, and recurrence revealed no significant differences, (P<0.05), while a significant difference was found among cases who had a family history (P<0.001). The detailed findings and associations between appearance of MSI markers in endometrial carcinoma against clinical and prognostic characteristics of the studied group are shown in (**Tables 1-6**).

Table 1. Appearance of Microsatellite Instability (MSI) markers in Endometrial Carcinoma

Parameter	No.	%
Unaltered expression of all markers	**35**	**55.6**
Loss of expression	**8**	**12.7**
MLH1/PMS2 loss of expression	**17**	**27.0**
MSH2/MSH6 loss of expression	**2**	**3.2**
Isolated MLH1 loss of expression	**1**	**1.6**

Table 2. Appearance of Microsatellite Instability (MSI) markers in Endometrial Carcinoma and Its Correlation with Tumor Stage

Parameter	Tumor (T) Stage								Total
	I		II		III		IV		
	No.	%	No.	%	No.	%	No.	%	
Unaltered expression of all markers	21	60.0	7	20.0	7	20.0	0	0.0	**35**
Loss of expression	4	50.0	3	37.5	0	0.0	1	12.5	**8**
MLH1/PMS2 Loss of expression	12	70.6	3	17.6	2	11.8	0	0.0	**17**
MSH2/MSH6 Loss of expression	1	50.0	0	0.0	1	50.0	0	0.0	**2**
Isolated MLH1 loss of expression	1	100.0	0	0.0	0	0.0	0	0.0	**1**
Total	**39**	**61.9**	**13**	**20.6**	**10**	**15.9**	**1**	**1.6**	**63**
P. value = 0.380 not significant									

Table 3. Appearance of Microsatellite Instability (MSI) Markers in Endometrial Carcinoma and Its Correlation with Nodal Stage

Parameter	Nodal (N) Stage						Total
	N0		N1		N2		
	No.	%	No.	%	No.	%	
Unaltered expression of all markers	35	100.0	0	0.0	0	0.0	**35**
Loss of expression	7	87.5	1	12.5	0	0.0	**8**
MLH1/PMS2 Loss of expression	13	76.5	4	23.5	0	0.0	**17**
MSH2/MSH6 Loss of expression	1	50.0	0	0.0	1	50.0	**2**
Isolated MLH1 loss of expression	1	100.0	0	0.0	0	0.0	**1**
Total	**57**	**90.5**	**5**	**7.9**	**1**	**1.6**	**63**
P. value <0.001 significant							

Table 4. Appearance of Microsatellite Instability (MSI) Markers in Endometrial Carcinoma and Its Correlation with FIGO stage

Parameter	FIGO Stage								Total
	I		II		III		IV		
	No.	%	No.	%	No.	%	No.	%	
Unaltered expression of all markers	20	57.1	8	22.9	7	20.0	0	0.0	**35**
Loss of expression	4	50.0	3	37.5	0	0.0	1	12.5	**8**
MLH1/PMS2 Loss of expression	12	70.6	4	23.5	1	5.9	0	0.0	**17**
MSH2/MSH6 Loss of expression	1	50.0	0	0.0	1	50.0	0	0.0	**2**
Isolated MLH1 loss of expression	1	100.0	0	0.0	0	0.0	0	0.0	**1**
Total	**38**	**60.3**	**15**	**23.8**	**9**	**14.3**	**1**	**1.6**	**63**
P. value = 0.300 not significant									

Table 5. Appearance of Microsatellite Instability (MSI) Markers in Endometrial Carcinoma and Its Correlation with FIGO stage

Parameter	FIGO Grade						Total
	I		II		III		
	No.	%	No.	%	No.	%	
Unaltered expression of all markers	15	42.9	16	45.7	4	11.4	**35**
Loss of expression	3	37.5	5	62.5	0	0.0	**8**
MLH1/PMS2 Loss of expression	7	41.2	9	52.9	1	5.9	**17**
MSH2/MSH6 Loss of expression	1	50.0	1	0.0	0	50.0	**2**
Isolated MLH1 loss of expression	1	100.0	0	0.0	0	0.0	**1**
Total	**27**	**42.9**	**31**	**49.2**	**5**	**7.9**	**63**
P. value = 0.900 not significant							

Table 6. Appearance of Microsatellite Instability (MSI) Markers in Endometrial Carcinoma and Its Correlation Cervical Invasion, Adnexal Involvement, Lympho-vascular Invasion, Family history and Recurrence

Parameter	Cervical Invasion	Adnexal Involvement	Lympho-vascular Invasion	Family history	Recurrence
Unaltered expression of all markers(n=35)	12	5	2	0	6
Loss of expression (n=8)	4	0	0	4	3
MLH1/PMS2 Loss of expression (n=17)	3	0	2	2	2
MSH2/MSH6 Loss of expression(n=2)	1	1	0	1	1
Isolated MLH1 loss of expression (n=1)	0	0	0	0	0
Total (n=63)	20	6	4	7	12
P. value	0.450	0.110	0.800	<0.001*	0.410

*Significant

DISCUSSION:

In the present study we evaluated the Micro stability index of EC (endometrial cancer) in Iraqi sampling patients (N=63) who selected in medical city complex. In the present study, a statistically significant correlation was found between MMR expression status and nodal stage. Most patients in all categories do not have nodes (N0), but 23.5% of those with MSH2/MSH6 deletion did have. The single MSH2 deletion case exhibited elevated rates of nodal involvement in contrast to the unaffected group. We found that the abnormal expression of MSI in our community was 42.9% which is less than (44.0%) that reported by a Pakistani study carried by Hashmi A et al., in 2019 [19]. But it is relatively higher as compared to the revisions that done in other areas of the world. The occurrence of MSI+ endometrial malignancies varies relatively a bit. In a study carried in United States encompassing less than 5 hundred patients diagnosed with ECs (endometrial cancers), about one fifth of them presented with MSI+ tumors were. MSI+ tumors had more favorable survival even though they were associated with prognostically poor histologic criteria such as pathologic stage and grade [20]. MSI is known to be uniquely associated with the endometrioid histology, so that we excluded non-endometrioid endometrial tumors from the investigation [21]. A broad series of NRG oncology/gynecology group study allocated more than thousand patients into 4 mismatch repair (MMR) classes and revealed that MMR abnormalities were associated with bad prognostic variables including greater grade, myometrial invasion, and lympho-vascular invasion.

Conversely, there was no notable change in the survival of these patients, leading to the conclusion that immunological surveillance associated with MMR abnormalities may counterbalance the impact of adverse prognostic factors in these individuals [22]. In other investigation, MSI-high status was identified in 15.6% of endometrial malignancies, although no statistically significant results were seen. Differences between patients with MSI-high and MSI-stable cancers were identified following adjustments for stage, histology, and tumor grade in multivariate analysis [23].

Our results align with these findings, as we identified a relationship between MSI+ endometrial malignancies and elevated TNM/FIGO stages; however, no association was observed with disease-free survival. Histological characteristics of MSI-high tumors encompass poor differentiation and both intra-tumoral and peri-tumoral lymphocytic responses in colorectal malignancies; however, these findings are not validated in endometrial cancers.

A revision done in 2017 by Kunitomi et al., revealed that less than 3rd prevalence of microsatellite instability was seen in endometrial malignancies (EMs); however, the inclusion of non-endometrioid cancers in their analysis may account for this discrepancy [24].

Limitation of the study: This is the first study done in Iraq so we can't discuss the results with another local study.

CONCLUSIONS:

A significant prevalence of endometrioid tumors in our investigation had aberrant levels of MSI markers, predominantly indicating diminished MLH1/PMS2, and were not linked to hereditary cancer predisposition. A minority of cases exhibited a complete loss of all MSI indicators or an absence of MSH2/MSH6, which was substantially correlated with a family or individual history of malignancy.

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