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Assessment of PMS2 Expression in Iraqi Patients with Endometrial Cancer

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Abstract : Background: Endometrial carcinoma (EC) represented the sixth most common cancer amongst women worldwide.Postmitoticsegregation increased 2 (PMS2) is a gene that encrypts a protein that rolesin DNA mismatch repair (MMR).Objectives:To assessment the expression of the PMS2in endometrial tumors and knowing the extent of disease's progression through the interaction between the secretion on the surfaces of the pathological cells with the PMS2 marker , andFinding the relationship between age,stage and grade of tumors with expression of the PMS2 marker.Material and methods:Overall of seventy samples of paraffin embedded tissue blocks of diverse endometrium tissue cancerincluding 30 malignant with ages ranging from 30 to 70 years, 30 benign with ages from 20 to 60 years and 10 health endometrium biopsies as a control with ages ranging from 30 to 40 years. Results:The findings of this task demonstrated substantial variation in the expression of PMS2 between endometrial benign and malignant tumors ($P<0.001$). Furthermore, significant correlation was found between PMS2 with histological grade in malignant cases. There wasno significant variation in PMS2 expression with age and pathological stage. Conclusion:This allowed us to suggest that PMS2 hasadvantageous for managing of endometrial cancer in patients with DNAMMR.

Keywords: PMS2gene,Immunohistochemistry, Iraqi patients,Endometrial cancer, Postmitotic segregation increased 2.

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Introduction

Cancer is the major health issue around the world, in spite of the development in the diagnosis and therapy methods(1).Early stages of carcinogenesis in tumors are influenced by epigenetic changes like DNA methylation(2).Endometrial cancer (EC) accounted for 2% of new cancer cases and 1% of deaths in 2020(3).In the United States (US) the expected incidence of EC in 2022 is 65,950 new cases with nearly 12,550 estimated deaths(4),and accounting for 6% of all female cancer cases, the fourth most prevalent cancer in women (5). In cancer, lymph node dissection is one of the most significant prognostic markers. Patients who have surgery for a gynecological cancer may be at risk for developing deep vein thrombosis if they undergone lymphadenectomy (6). Because of the vaginal bleeding not being correlated with menstrual period, it is often the first sign in most EC cases. About 10–15% EC in patient women is often detected at an early stage because it often has vaginal bleeding in abnormal time(7). EC has been divided into two types based on

differences in subsequent clinical outcomes and histology. The popular of EC cases are type I endometrioid and type IIEC non endometrioid(8).The incidence of endometrial cancer has been rising yearly and increasing with age in recent years.Obesity is a global health concern because of its tendency to rise in both developed and developing countries(9). Everyday rising rates of obesity are having an impact on all populations at all ages (10). According to Iraqi Cancer Registry 2020, the country's uterine percentage is undefined (3.23%, 2.92/100,1000 FP). Severalof The following risk factors are linked to the occurrence of endometrial cancer:chronic estrogen stimulation,alterations in lifestyle, such as diabetes, obesity, and hypertension, and genetic mutations(11). Development of EC is a multi-factorial and multi-step process,with an early manifestation of vaginal bleeding that happened after menopause about 70 percentages of patients are diagnosed by fractional curettage, at an early stage(12). EC also diagnosed by ultrasound imaging(13), endometrial biopsy(13), hysteroscopy(14), and magnetic resonance imaging (MRI)(15). Approximately 5–15% of cases of Lynch syndrome (LS) are caused by the PMS2 gene(16). Cancers that have a single absence of PMS2 expression on immunohistochemistry (IHC) are linked to PMS2 germline mutation(17). Individuals who carry any harmful mutationtypically found in one of the MMR genes believed to have a similar likelihood of getting various types of cancer. The two primary types of cancer mentioned are colorectal cancer (CRC) and endometrial cancer(18).

Material and Methods

The research was carried out during the period between 2023 and 2024 at the biology department of the college of science at Baghdad University and the pathology department of the college of medicine at Al-Nahrain University. The endometrium tissue samples that were used in this study were in form of paraffin blocks and was gathered from Al-Yarmouk Teaching Hospital, Teaching Laboratories of Medical City, Al- Karama Teaching Hospital, Al-Imamain Al-Kadhimain Medical City, and Forensic Medicine Department in Baghdad for the years (2020-2023). A total of 70 paraffin blocks containing endometrial tissues were used in this experiment, including 30 malignant , 30 benign and 10 health endometrium biopsy.Positive control and endometrium tissues samples were sectioning of 5 µm thickness and stained with alcoholic eosin and harrishematoxylin stain (19)for histopathology detections and immunohistochemistry stain PMS2 by using abcam data sheet to identify the malignancy, respectively. The scoring system for PMS2 expression was done according to (20) and the results were assessed and read by a specialist pathologist. Negative (0, no staining), Low 1 (<50%), Intermediate 2 (≥60%) and High 3 (≥80%) .

Statistical analyses

The statistical analysis System SPSS-28 (Statistical Package for Social Sciences version 26). The data were analyzed for normality of distribution using Shapiro-wilk and presented as mean ± standard deviation (SD) in addition to median and range according to normally distribution data were compared analysis of variance (ANOVA), while those not normally distributed were compared using Mann Whitney U Test. Categorical data were presented as number and its percentage and comparison done using Yates chi square test. Pearson correlation was

used to compare markers expression with age and between them.While Kruskal-Wallis Test was used to correlate markers with stage & grade of malignancy. P value ≤ 0.001 was considered highly significant andP≤ 0.05 was significant(21).

Results and Discussion

1- Association of IHC expression of PMS2 between benign and malignant cases

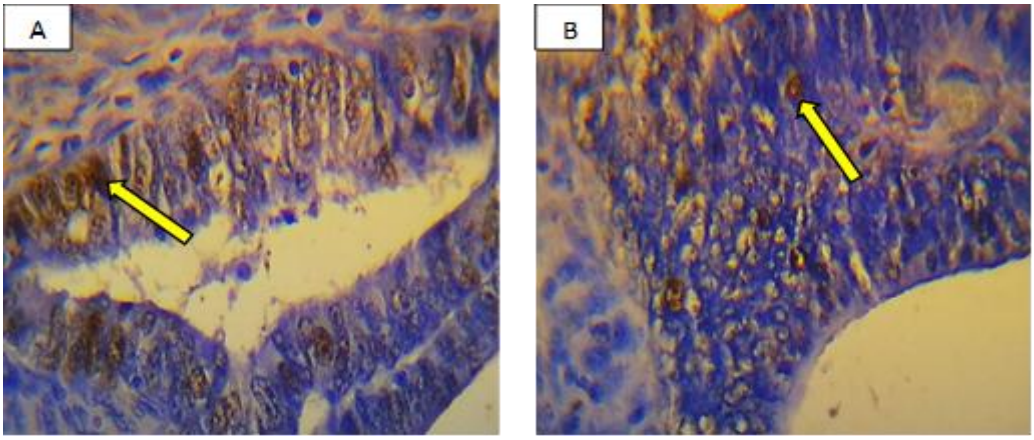
The positive expression of PMS2 was shown as brown staining.The present study found highly significant correlation between PMS2 expression with benign and malignant cases , P= <0.001, while it was expressed negatively or not at all in 100% of normal endometrium tissues.(Table 1)(Figure.1,2).

Table (1): Association of IHC expression of PMS2 between benign and malignant cases.

Expression		Benign N=30	Malignant N=30	P value
PMS2 (%)	Mean±SD	37.5±10.81	71.83±9.24	**<0.001***
	Median (Range)	35 (10-50)	70 (50-90)	

*P value by Mann Whitney test

The current study found that PMS2 was expressed positively in most malignant cases accounting for approximately 71.83±9.24 of all cases. There were significant correlation between expression of PMS2 with benign and malignant cases (P=<0.001).This outcome comes to an agreement with (22) who showed that PMS2 was highly expressed in tumor types including pancreatic cancer. A study by (23) who stated in their study that loss of MMR protein expression was seen in singles or clusters of morphologically normal nonneoplastic endometrial glands. This in line with the results of the present study. A study by (24) founding that PMS2 expression was (0-5 %) of normal in gastric tumor and this consistent with current study.



Figure(1): Immunohistochemical assessment of PMS2 for malignant cases

A:Cross section of endometrium tissue show high nuclearexpression of PMS2 score 3 in Endometrial endometrioid adenocarcinoma,(40 X). B:Cross section of endometrium tissue show nuclear expression of PMS2 score 2 in Endometrial endometrioid adenocarcinoma/villoglandular variant,(40X) (arrows).

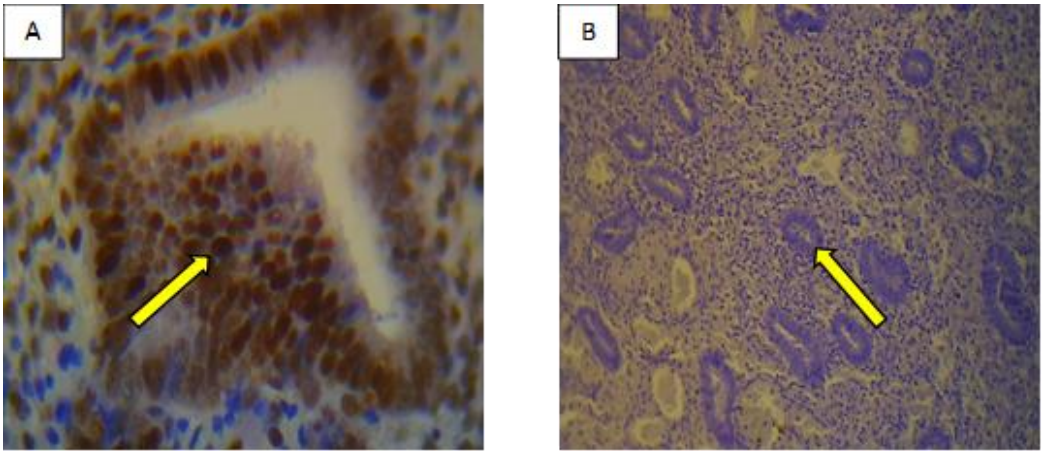


Figure (2): Immunohistochemical assessment of PMS2 for benign cases

A: Cross section of endometrium tissue show nuclear expression of PMS2 score 2 in Hyperplastic polyp. (40X). B: Cross section of endometrium tissue show negative control with no expression of PMS2 (100X) (arrows).

2-Association of IHC score of PMS2 with benign and malignant cases

This study shows highly significant differences (P<0.001) between the score of PMS2 with benign and malignant cases. (Table 2).

Table (2): Association of IHC score of PMS2 with benign and malignant cases

Parameter	Score	Benign N=30 N (%)	Malignant N=30 N (%)	P value
PMS2	1	30 (100)	2 (6.6)	**<0.001***
	2	0 (0.0)	20 (66.7)	
	3	0 (0.0)	8 (26.7)	

*P value by Yates chi square test

This study shown highly significant variances between the score of PMS2 with malignant and benign cases. This consistent with (22) who founding in their study that PMS2 was highly expressed in cancer types including pancreatic tumor. A study by (25) suggest that PMS2 may provide a probable dependable biomarker for Sporadic Colorectal Cancer (CRC) classification by combined immunohistochemical and messenger RNA analysis.

3- Association of IHC expression of PMS2 with age in benign and malignant groups

The present study found no significant correlation between PMS2 expression with patient's ages in all studied groups (P=0.883) for malignant cases (Table 3.1), and (P=0.890) for benign cases (Table 3.2).

Table (3.1): Association of IHC expression of PMS2 with age in malignant groups

Parameter		< 40 yr N=1	40-49 yr N=5	50-59 yr N=9	≥60 yr N=15	P value
PMS2 (%)	Mean±SD	---	70±0	71.11±11.67	72.33±9.61	0.883*
	Median (Range)	---	70 (70-70)	70 (50-90)	70 (50-90)	

*P value by Kruskal-Wallis Test, ** P value by ANOVA, only one patient in age group <40 yr, so not involved in statistics

Table (3.2): Association of IHC expression of PGK1 with age in benign groups

Parameter		< 40 yr N=9	40-49 yr N=13	50-59 yr N=4	≥60 yr N=4	P value*
PMS2 (%)	Mean±SD	37.22±12.53	36.15±11.75	37.5±6.45	42.5±8.66	0.890*
	Median (Range)	30 (20-50)	35 (10-50)	37.5 (30-45)	45 (30-50)	

*P value by Kruskal-Wallis Test

In this study there were no significant variances between PMS2 expression and age for malignant cases compared to the benign group. According to (23) showed no statistically significant association was found between the age of patients and MMR IHC proteins expression , which is consistent with the outcomes of this study.

4 -Association of IHC expression of PMS2 with pathological stage

This study revealed no significant association (P =0.815) between PMS2 positive expression and pathological stage in malignant group (Table 3).

Table (4):Association of IHC expression of PMS2 with pathological stage

Parameter		Stage I N=21	Stage II N=3	Stage III N=6	P value*
PMS2 (%)	Mean±SD	71.9±9.15	71.67±18.93	71.67±4.08	0.815*
	Median (Range)	70 (50-90)	80 (50-85)	70 (70-80)	

*P value by Kruskal-Wallis Test

The present study found no significant correlation between PMS2 expression and stage in malignant group. A study by (23) found that no statistically significant correlation between FIGO stage and MMR IHC protein expression, this in line with the finding of the current study.

-5 Association of IHC expression of PMS2 with histological grade

This study found highly significant association (P= <0.008) between PMS2 positive expression and tumor grade in malignant group (Table 4).

Table(5): Association of IHC expression of PMS2 with tumor grade in malignant group

Parameter		Grade I N=22	Grade II N=6	Grade III N=2	P value*
PMS2 (%)	Mean±SD	69.09±8.54	77.5±6.12	85±7.07	**0.008**
	Median (Range)	70 (50-90)	80 (70-85)	85 (80-90)	

*P value by Kruskal-Wallis Test

In this study there was significant variations between grade in malignant group and PMS2 expression. A study by (26) revealed that statistically significant association between MMR IHC protein expression and grade of EC , these are consistent with the results of this study. According to (25) found that PMS2 expression was associated with the cancer differentiation grade , this in line with present study.

Conclusion

The high expression of PMS2 was found in most malignant cases, but it was weak in most of benign samples, while no expression was seen in normal endometrium tissue samples. A significant association was found between PMS2 with histological grade in malignant cases. This allowed us to suggested that PMS2 may be useful in themanagement of endometrial tumor in patients with DNA mismatch repair.

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