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RELATIONSHIP OF IMMUNOHISTOCHEMICAL EXPRESSION OF MISMATCH REPAIR GENE PRODUCTS AND CLINICOPATHOLOGICAL FEATURES IN PATIENTS WITH LOW-GRADE ENDOMETRIAL CANCER

Marija Joksimovic[1], Nikola Jankulovski[2], Gordana Petrusevska[3], Biljana Ognenoska Jankoska[4], Beti Zafirovska Ivanovska[5], Saso Stojcevski[1], Igor, Alulovski[1], Mile Tanturovski[1], Vladimir Joksimovic[2]

[1]University Clinic for Gynecology and obstetrics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, N. Macedonia,

[2]Clinic for Abdominal surgery, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia,

[3]Institute for pathology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia,

[4]Institute for Radiology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia,

[5]Institute for epidemiology and statistics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia

Abstract

Background: This study examines the relationship between mismatch repair (MMR) gene expression and clinicopathological features in patients with low-grade endometrial cancer (EC).

Methods: A prospective cohort of 40 patients with histologically confirmed low-grade EC underwent immunohistochemical analysis to determine MMR status. Clinical data, including age, body mass index (BMI), menopausal status, parity, and comorbidities, were collected. Histopathological evaluations assessed myometrial invasion,lymphovascular invasion and disease stage.

Results: MMR deficiency (MMRd) was identified in 35% of patients, predominantly associated with MLH1/PMS2 loss. No significant associations were found between MMR status and clinical characteristics such as age, BMI, or comorbidities. However, MMRd tumors exhibited a significantly higher prevalence of myometrial invasion over 50% (85.71% vs. 38.46%, p=0.0042) and lymphovascular invasion (71.43% vs. 19.23%, p=0.00114). Additionally, MMRd cases were more frequently associated with advanced disease stages, particularly in stage IIIC (28.57% vs. 7.69%, p=0.078).

Conclusion: The importance of MMR status in the biological behavior of low-grade endometrial cancer is highlighted in this study. The strong correlation between MMR deficiency and aggressive histopathological features such as increased myometrial and lymphovascular invasion, highlights the need to integrate MMR testing into clinical practice, even if clinical parameters showed no significant association with MMR expression. These results suggest that MMRd may be a useful prognostic indicator that requires more research to improve patient outcomes and treatment approaches for low-grade endometrial cancer.

Keywords **:** endometrial cancer, low grade, mismatch repair

Introduction

Through the correction of errors in DNA replication, the prevention of recombination between non-identical DNA sequences, and their involvement in responses to DNA damage, mismatch repair (MMR) mechanisms are essential for maintaining genetic stability. Initially, a tumor molecular phenotype named mismatch repair deficient (MMRd) was found in patients with germline mutations and is known as Lynch syndrome. The lifetime risk of endometrial cancer (EC) in patients with Lynch syndrome (LSy) is 60%. But this specific molecular genetic alteration, which is the result of a defect in MMR genes (MLH1, PMS2, MSH2 and MSH6) is also found in sporadic tumors which are named as mismatch repair deficient (MMRd) tumors or Lynch-like syndrome tumors. According to the available data, the rate of MMRd EC ranges around 25-40%.[1,2] In the majority of cases, the occurrence occurs

sporadically in the endometrial tissue itself, most often as a result of methylation of the MLH1 promoter region and resulting epigenetic silencing of MLH1. Less commonly, MMR deficiency results from the loss of expression of other MMR genes such as MSH2, MSH6 or PMS2.[3]

Testing for MMR deficiency can be done through immunohistochemical analysis of MMR proteins or through MSI testing. Both methods have comparative sensitivity and show a concordance of 96%. MMR immunohistochemistry as an advantage offers the detection of the presence or absence of the four MMR proteins in cancer cells, is a cheaper method, more accessible to pathologists, has the possibility of repeated external audit of the quality of the analyses, allows correlation with morphology and enables the identification of the defective protein, directing thus the possible further investigations. MSI testing detects differences in the length of selected microsatellites resulting from indel errors between normal and tumor cells. MSI testing is performed on DNA extracted from tumor tissue and is more expensive than the MMR IHC test.

In addition, the interpretation of the test requires a high level of expertise because the changes seen in EC are more subtle and challenging to interpret than those in colon cancer and do not provide information about the affected gene.[3,4]

The indications for MMR IHC in EC include: 1) Screening for LSy- It is believed that one in every 250-300 persons has LS, and more than 95% of these people are ignorant of their cancer risk. EC is frequently the first or so-called sentinel cancer, and so provides an opportunity to diagnose familial LS in a family. Patients with LSy who have received EC may acquire other types of cancer, and EC typically predates subsequent diseases such as colon cancer by about a decade.

Diagnosis of LS in a family enables surveillance and preventive interventions that greatly reduce mortality from later malignancies related with LS; 2) molecular diagnosis of EC: According to the TCGA classification,[1] MMR IHC/MSI testing is required in all cases to identify the hypermutated MMRd/MSI subtype, which has particularly significant implications for management; such tumors are unlikely to respond to conservative treatment with progesterone, show a higher likelihood of invasion of the lymphovascular space that warrants sentinel lymph node biopsy or other nodal procedure, and chemotherapy does not result in significant survival benefit 3) predictive tests: MMRd tumors are amenable for targeted therapy with immune checkpoint inhibitors.[5]

According to the guidelines of ESGO and the International Society of Gynecological Pathology - The International Society of Gynecological Pathology (ISGyP), universal testing of MMR/MSI status is recommended for all endometrial cancers, regardless of the patient's age and histological type.

Such a recommendation for universal MMR/MSI testing according to available resources is also provided by other associations, such as the Manchester International Consensus Group recommendations. The preferred approach (widely available and cost-effective) is with immunohistochemistry testing (IHC) on adequately preserved tumor tissue.[6-8]

Aim

This study aimed to determine the rate of low-grade MMRd EC and to assess the relationships between MMR protein expression and clinicopathologic outcomes in patients with low grade endometrial cancer.

Materials and methods

Patients

The study was designed as a prospective, cohort, prognostic intervention study. It included 40 adult randomly selected patients with a histological diagnosis of low-grade endometrial cancer, confirmed by analysis of material from fractionated endometrial curettage. Inclusion criteria for entry were the above-mentioned histological diagnosis, signed informed consent, and preoperatively presumed early stage disease. Exclusion criteria were high-grade disease, presumptive high-stage disease, neoadjuvant oncological treatment, and anesthetically unfit patients.

Metods

Histopathological evaluations. Low-grade endometrial cancer was diagnosed microscopically on paraffin sections from curettage material (fractionated endometrial curettage) submitted to the Institute of Pathology and/or the Laboratory of Histopathology and Cytology of the Radiotherapy and

Oncology Clinic. After 24 hours of fixation, the samples were processed in an automatic tissue processor before being molded in paraffin. An automatic rotary microtome was used to cut 4-5 micron sections, which were then stained with basic histological staining Hemalun and Eosin. The MMR status was determined by immunohistochemical analysis on the same material. For this purpose, an automated PT LINK immunoperoxidase technique was used on an Agilent Technologies (CA, USA) autostainer using an En Vision FLEX visualization system.

A panel of 4 antibodies was used to determine MMR status: MLH-1 (Dako Monoclonal Mouse Anti-Human, Clone ES05) at a dilution of 1:50, MSH-2 (Dako Monoclonal Mouse Anti-Human, Clone FE11) at a dilution of 1: 50, MSH-6 (Dako Monoclonal Mouse Anti-Human, Clone EP49) at 1:50 dilution and PMS-2 (Dako Monoclonal Mouse Anti-Human, Clone EP51) at 1:50 dilution. Loss of nuclear expression in neoplastic cells of any of these antibodies (nuclear proteins) is classified as a deficiency of the MMR mechanism (dMMR). Staining was considered positive if any part of the tumor gave nuclear restaining. Nuclear staining of the surrounding mucosa and lymphocytes on the same sections were used as an internal positive control, while in the negative control the monoclonal antibody will be replaced with phosphate buffer pH 7.4.

Surgical treatment. According to the tumor board treatment decision, all patients were operated at the gynecological oncology department. The operative treatment consisted of an open approach with a total abdominal hysterectomy with bilateral salpingo-oophorectomy and a sentinel lymph biopsy of the pelvic lymph nodes according to the established work protocol of the department.

The histopathological analysis of the operative material was performed at the Institute of Pathology, Skopje. The disease was staged according to the FIGO classification system (FIGO 2018).

To realize the set objectives, data from the medical documentation on the clinical characteristics of the test subjects were used. These were age, parity, body mass index (BMI) menopausal status,uterine bleeding, endometrial thickness measured by ultrasound during the diagnostic period, family history of malignancies (breast, gynecological and colorectal), and comorbidities such as arterial hypertension and diabetes mellitus. The disease grade, depth of myometrial invasion, presence of lymphovascular invasion and the stage of the disease were evaluated from the postoperative histopathology.

Results

Mismatch repair deficient immunohistochemical status (MMRd) was confirmed in 14 patients (35%) against 25 mismatch repair proficient (MMRp) (65%). Among them, the largest part, i.e. 13 cases, were with MLH1/PMS2 deficiency, PMS2 isolated loss in 1, MSH2/MSH6 in 2, while isolated loss of MSH6 was not identified.

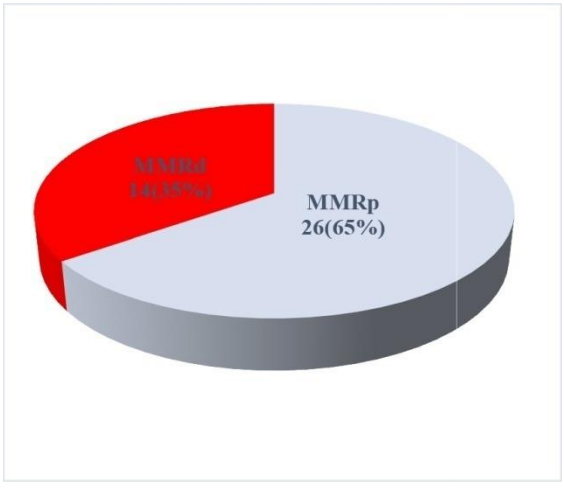

Figure 1. MMR status distribution

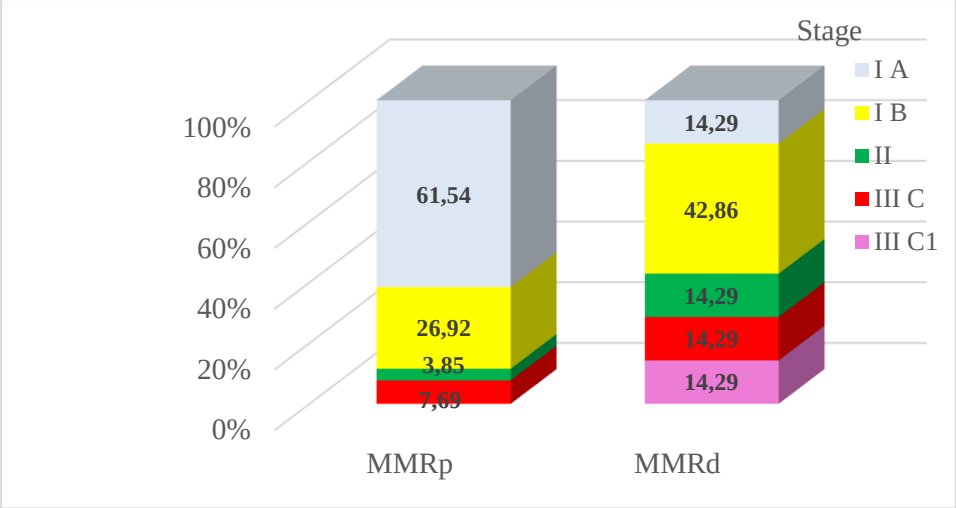

Figure 2. Distrubution of MMR profiles across disease stages

The study patients had a mean age of 61.5 years (range 45-82). The average BMI (32.59 kg/m2 ±6.9 kg/m2) ranged from 19 to 53. Thirty-three (82.5%) of the patients were postmenopausal, with 7 individuals in the reproductive and perimenopausal stages (17.5%). 36 (90%) of responders provided positive anamnestic knowledge regarding abnormal vaginal bleeding. A positive family history of gynecological, colorectal, and breast cancer was found in 25% of the patients (10).

Parity study revealed that 70% of the patients had ≤2 children, while 30% (12 responders) had more than 2 children. Thirty-one patients (77.5%) had arterial hypertension, including one with a cerebrovascular episode (2.5%), and one with an aortic aneurysm (2.5%). Diabetes mellitus was diagnosed in 16 patients (40% of the cases).
The initial diagnostic ultrasonography evaluation of endometrial thickness revealed that the average thickness measured in millimeters (mm) was (15.72±6.7)(min 6-max 36)[14.5(10.5-20). Endometrial thickness was stratified into two groups: ≤ 20 mm and > 20 mm, with 31 (77.5%) and 9 (22.5%) participants, respectively.

The stage distribution yielded the following results: 18 patients (45%) were classified in stage IA, 13 (32.5%) in IB, 3 (7.5%) in II, and 6 (15%) in IIIC. In terms of grade, 19 patients (47.5%) were diagnosed with grade 1, while 21 patients (52.5%) had grade 2 endometrial cancer. The histopathological evaluation of myometrial invasion indicated that 18 patients (45%) had less than 50% invasion, whereas 32 patients (55%) exhibited more than 50% invasion. Lymphovascular invasion was found in 15 patients (37.5%), while 25 patients (62.5%) showed no signs of lymphovascular invasion.

Comparison of MMRdeficient/MMR proficient low-grade endometrial carcinomas in terms of clinical and histopathological factors showed a statistically significant difference in MMR expression in relation to myometrial invasion (p=0.0042), lymphovascular invasion (p=0.00114) and with disease stage (p=0.013). No statistically significant difference was found between MMR deficient and MMR proficient profiles in terms of patient age, body mass index, family history, symptomatology, menopausal status, presence of comorbidities and parity.

In MMRd EC, myometrial invasion over 50% and lymphovascular invasion were registered significantly more often (85.71% vs 38.46%, 71.43%, vs 19.23% respectively).

Regarding the stage of the disease, a significantly greater proportion of patients in IA stage were MMRp compared to MMRd for the same (61.54% vs 14.29%, p=0.0042), and the distribution in IIIC stage also showed statistical significance (7.69% vs 28.57%). , p=0.078). The MannWhitney test with a significance level of 0.005 rejected the hypothesis of equal distribution of MMR status across stages.

Table 1. This table summarizes the key findings from the study, allowing for a clear comparison between MMR expression groups across the clinicopathological parameters.

Variable		**MMR status**			**p-level**
		n	MMRp	MMRd	
Age **(years)**	mean ± SD		59.3 ± 9.2	64.6± 7.3	t=1.84
	min- max		45 – 74	54 – 82	p=0.074
Grade	1	18	14 (58.33)	4 (30.77)	X^2=2.6
	2	19	10 (41.67)	9 (69.23)	p=0.11
Miometrial invasion	MI < 50%	18	16 (61.54)	2 (14.29)	X^2=8.2
	MI > 50%	22	10 (38.46)	12 (85.71)	****p=0.0042**
Limphovascular invasion	present	15	5 (19.23)	10 (71.43)	X^2=10.6** **p=0.00114**
Stage	I A	18	16 (61.54)	2 (14.29)	Fisher´s exact
	I B	13	7 (26.92)	6 (42.86)	***p=0.013**
	II	3	1 (3.85)	2 (14.29)	
	III C	4	2 (7.69)	2 (14.29)	
	III C1	2	0	2 (14.29)	
Body mass index (BMI)	mean ± SD		32.77 ± 7.8	32.23 ± 5.2	t=0.22
	min- max		19 – 53	25 – 42	p=0.82
	median (IQR)		30.5 (28 – 39)	31 (28 – 36)	
Endometrial thickness	mean ± SD		14.42 ± 7.3	18.14 ± 4.7	t=1.7
	min- max		6 – 36	11 – 25	p=0.09
	median (IQR)		12 (10 – 17)	20 (14 – 22)	
Endometrium grupus	≤ 20	31	22 (84.62)	9 (64.29)	Fisher´s exact
	> 21	9	4 (15.38)	5 (35.71)	p=0.23
Parity	≤ 2	28	18 (69.23)	10 (71.43)	p=1.0
	> 2	12	8 (30.77)	4 (28.57)	
Postmenopausal status	yes	33	19 (73.08)	14 (100)	p=0.074

Uterine bleeding	yes	36	23 (88.46)	13 (92.86)	p=1.0
Positive family history	yes	10	8(30.77)	2(14.29%)	Fisher´s exact p=0.45
Arterial hypertension	yes	29	18 (69,23)	11 (78,57)	Fisher´s exact p=0.46
	no	9	7 (26,92)	2 (14,29)	
	CVI	1	1 (3,85)	0	
	aneurism	1	0	1 (7,14)	
Diabetes mellitus	да	16	11 (42.31)	5 (35.71)	X^2=0.05 p=0.82
	не	23	15 (57.69)	8 (57.14)	
	missing	1	0	1 (7.14)	

X^2(Chi-square test); t(Student t-test)

*sig p<0.05, **sig p<0.01

Discussion

The findings from this study provide significant insights into the clinical and histopathological implications of mismatch repair (MMR) status in endometrial cancer. The results indicate a notable prevalence of mismatch repair deficiency (MMRd) in 35% of the patients, while 65% were classified as mismatch repair proficient (MMRp). This distribution is consistent with existing literature that highlights the importance of MMR status in various cancers, particularly those associated with hereditary syndromes like Lynch syndrome. Understanding these differences is critical to tailoring therapeutic approaches and improving patient outcomes.

The rate of 35% is toward the upper limit of the published literature,[1,2] which is expected given that the MMRd profile is most prevalent in endometrioid endometrial carcinomas. Otherwise, this rate is almost twice as high as that reported for colorectal cancers. MMR deficiency [MMR deficient (MMRd)] is due to microsatellite instability characterized by a high level of gene mutations.[9]

The MMR protein product has been extensively investigated as a predictive and prognostic marker for endometrial cancer.

Published studies show that MMR deficiency can predict the presence of disease with high-risk features, such as advanced age, advanced disease stage (lymph node status), and uterine risk factors (depth of myometrial invasion, cervical stromal invasion, size of tumor, lymphovascular invasion).[10-15]Several studies associate MMRd EC with lower histological grade, while a larger number of studies show higher grade among MMRd EC.[16-19] MMRd tumors have also been analyzed for association with FIGO stage. A greater number of studies associated MMRd EK with higher stage disease (58–67% of higher stage tumors were MMRd) compared to MMRp EK (18–41%).[20-23] Published data on the association with lymphovascular invasion, lymph node invasion, and the likelihood of metastasis,show higher rate of lymphovascular invasion among MMRd EK and a higher probability of metastasis compared to MMRp EK.[24] The mean age of participants in this study was 61.5 years, which aligns with the typical demographic for endometrial cancer patients.

The age range of 45 to 82 years reflects the disease's occurrence predominantly in postmenopausal women. The results of our analysis did not show statistical significance for the association of age with MMR status, although the percentage of older patients was higher among MMRd EC. The BMI distribution indicates a prevalence of obesity, which is a well-established risk factor for endometrial cancer.

The observed 25% positive family history of gynecological, colorectal, and breast cancers in the study population aligns with the implications of MMRd status, as these patients may be at risk for hereditary cancer syndromes. Furthermore, the high prevalence of comorbidities, including arterial hypertension and diabetes, suggests that the clinical management of endometrial cancer patients should consider these factors, as they could impact treatment choices and patient outcomes.

No significant differences were observed in patient demographics such as age, BMI, or menopausal status, nor endometrial thickness, parity, family history and comorbidities.

This lack of association suggests that MMR status may play a more critical role in tumor biology than in traditional demographic factors. It emphasizes the need for further research to elucidate the biological mechanisms linking MMR deficiency to disease progression and outcomes. Histopathological analysis revealed critical insights into myometrial invasion and lymphovascular invasion. The finding that MMRd cases frequently exhibited myometrial invasion over 50% (85.71% vs. 38.46% for MMRp) emphasizes the possible aggressive nature of MMRd tumors. Additionally, the significant prevalence of lymphovascular invasion in MMRd cases highlights a potential mechanism by which these tumors may metastasize more readily.

The stage distribution analysis revealed that a greater proportion of MMRp patients were in the earlier stage (IA) compared to MMRd patients. This finding, alongside the significant differences in myometrial and lymphovascular invasion, suggests that MMRd tumors may present at a more advanced stage or have more aggressive characteristics. The association of MMRd status with later-stage disease (notably IIIC) may influence treatment strategies, as MMRd tumors might respond differently to standard therapies, including chemotherapy and immunotherapy.

Conclusion

In conclusion, the results of this study highlight the critical role of MMR status in the clinical and pathological characterization of endometrial cancer. The significant differences in myometrial invasion, lymphovascular invasion, and stage distribution underscore the need for personalized treatment strategies based on MMR profiling. As the landscape of endometrial cancer treatment evolves, integrating MMR status into clinical practice will be essential for optimizing patient outcomes. Continued research in this area promises to enhance our understanding of endometrial cancer biology and improve therapeutic approaches for affected patients.

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