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ORIGINAL RESEARCH

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Mismatch repair proteins evaluation in endometrial carcinoma: clinicopathological features and prognostic implications

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Abstract

Endometrial carcinoma is a prevalent cancer affecting women worldwide. Mismatch repair proteins (MMR) play a crucial role in maintaining genomic stability and preventing the accumulation of mutations. The evaluation of MMR proteins can aid in the identification of mismatch repair deficient (MMRd) tumors, which have distinct clinicopathological features and prognostic implications. This study aims to analyze the expression of MMR proteins in a cohort of 96 endometrial carcinoma cases collected from the pathology department archive at a tertiary center between 2010 and 2022. Of the 96 cases, 36 were classified as MMRd, which encompassed various subtypes, including endometrioid, mixed mullerian tumor (MMMT), and papillary serous carcinoma. The MMRd tumors exhibited distinct histopathological characteristics, such as low-grade differentiation and lymphoepithelioma-like patterns. Immunohistochemical analysis revealed paired loss of MLH1 and PMS2 in the majority of cases, while loss of MSH2 and MSH6 was observed in a smaller subset. Additionally, in a subset of patients had a familial history of cancer, indicating potential hereditary factors contributing to MMRd. In terms of prognostic markers, MMRd tumors exhibited higher rates of Estrogen Receptor (ER)/Progestron Receptor (PR) positivity and wild type p53 staining. Overall, our findings suggest that the evaluation of MMR proteins in endometrial carcinoma can provide valuable insights into the clinicopathological characteristics and prognostic implications of MMRd tumors.

Keywords

Endometrial carcinoma; Mismatch repair proteins; Clinicopathological characteristics; MMR-deficient tumors; Immunohistochemistry; Prognosis

1. Introduction

Endometrial carcinoma is the most common gynecological malignancy, accounting for a significant proportion of cancer-related deaths among women globally. According to the World Cancer Research Fund, endometrial carcinoma ranks as the sixth most commonly diagnosed cancer in women worldwide, with an estimated 382,069 new cases reported in 2018 [1, 2]. However, it is important to note that the prevalence of endometrial carcinoma varies across different geographical regions.

Corpus uteri cancer ranked as the fourth most common cancer overall among Saudi women in 2020 with 494 cases, or 6.3% of all cancer cases diagnosed among females in Saudi Arabia [3]. Moreover, retrieved data indicate an increasing incidence of the disease. Alghamdi IG *et al.* [4] published a retrospective study conducted in Riyadh, the capital city of Saudi Arabia, central region, reported a significant rise in endometrial carcinoma cases between 2001 and 2008, with an average annual percentage change of 4.7%. Similarly, another study conducted in Jeddah, western region of Saudi Arabia, showed an increasing trend in endometrial carcinoma cases over a 10-year period (2001–2010), with an annual percentage change of 5.7% [5].

The factors contributing to the rising prevalence of endometrial carcinoma in Saudi Arabia may include changes in lifestyle, obesity rates and hormonal imbalances. Obesity, in particular, has been identified as a significant risk factor for endometrial carcinoma. Saudi Arabia has witnessed a rapid increase in obesity rates over the past few decades, with a prevalence of obesity estimated at 35.5% among Saudi women in 2020 [6]. This increase in obesity rates could potentially contribute to the higher prevalence of endometrial carcinoma in the country.

The identification and characterization of molecular alterations in endometrial carcinoma have led to improved diagnostic and therapeutic strategies. One of the key molecular alterations observed in endometrial carcinoma is the deficiency in mismatch repair proteins (MMR) [7]. MMR proteins are responsible for repairing DNA replication errors, maintaining

genomic stability, and preventing the accumulation of mutations [8]. MMR deficiency results in a state of genomic instability, leading to the development of MMR-deficient (MMRd) tumors [9]. MMRd tumors have distinct clinicopathological features and prognostic implications [10]. This study aims to evaluate the expression of MMR proteins in a cohort of endometrial carcinoma cases and analyze the associated clinicopathological characteristics and prognosis [11].

Microsatellite instability (MSI) is a distinct molecular pathway associated with the pathogenesis of endometrial carcinoma. MSI is characterized by the presence of alterations or mutations in DNA microsatellites, which are repetitive sequences scattered throughout the genome. These errors can result from mutations or epigenetic silencing of MMR genes, such as *MLH1*, *MSH2*, *MSH6* and *PMS2*. The loss of MMR function impairs the ability to correct replication errors, leading to genomic instability and promoting the development of tumors [12]. MSI is most commonly observed in hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, where germline mutations in MMR genes are inherited. However, MSI can also occur sporadically in various other tumor types, including endometrial, gastric, ovarian and colorectal cancers. The prevalence of MSI in endometrial carcinoma varies, with studies reporting rates ranging from 15% to 30% [13]. Endometrial carcinoma is a heterogeneous malignancy, and the assessment of MMR protein status has emerged as a critical determinant of prognosis and management. Understanding the pathogenesis of MSI in endometrial carcinoma is crucial for identifying potential therapeutic targets and improving patient outcomes. This study aimed to evaluate the expression of MMR proteins in endometrial carcinoma cases that was diagnosed in a tertiary care center in the Western Region of the kingdom, by immunohistochemical methods of detection of this mutation. In addition to investigate their clinicopathological characteristics and prognostic implications.

2. Methods

A retrospective analysis was conducted on 96 endometrial carcinoma cases collected from the pathology department archive at King Abdulaziz University Hospital between 2010 and 2022. Patients who had a confirmed diagnosis of endometrial carcinoma were enrolled. Exclusion of cases included samples with inadequate or poor-quality formalin-fixed paraffin-embedded tissue samples that were unsuitable for reliable immunohistochemical analysis. Additionally, cases that lacked comprehensive clinicopathological data were not considered.

Formalin-fixed paraffin-embedded tissue samples were retrieved, and MMR protein expression was evaluated using immunohistochemistry. The MMR proteins assessed included MLH1, PMS2, MSH2 and MSH6. Clinicopathological data, including age, tumor size, tumor subtype, histopathological grade, myometrial involvement, lower uterine segment involvement, presence of clear cell component, ER/PR status, p53 status and familial history of cancer, were recorded for the MMRd tumors.

The authors reviewed all the cases histopathologically, rendered a diagnosis based on the WHO diagnostic entities, and compared it with the original diagnosis. Eventually, the best tumor area was circled for tissue microarray processing. Utilizing tissue cylinders with a diameter of 0.6 mm, representative tumor regions were punched of each donor-tissue block and transferred into recipient paraffin blocks.

Sections derived from formalin-fixed, paraffin-embedded tissue underwent standard immunohistochemical staining procedures. Ventana antibodies, specifically anti-MLH1 (clone M1), anti-MSH2 (clone G219-1129), anti-PMS2 (clone A16-4) and anti-MSH6 (clone SP93), were used in the immunohistochemical analysis. Two qualified pathologists examined the staining pattern of MMR proteins MLH1, MSH2, MSH6 and PMS2. The presence of MMR proteins is assessed through nuclear staining of tumor cells. Positive staining suggests the MMR system is intact, often corroborated by positive staining in adjacent non-tumor cells (smooth muscles and lymphocytes) serving as an internal control. Conversely, a complete absence of nuclear staining in tumor cells, despite positive staining in non-tumor cells, indicates MMR deficiency. Cases with one or more MMR proteins losing their staining were deemed MMR deficient, whereas cases with complete staining of all MMR proteins were deemed MMR proficient.

Statistical analysis was performed using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA). Two-sided p-value < 0.05 was considered significant.

3. Results

Of the 96 cases analyzed, 36 (37.5%) were classified as MMRd based on the loss of one or more MMR proteins. Among the MMRd tumors, 31 (86.1%) were of the endometrioid subtype, while 3 (8.3%) were mixed mullerian tumors (MMMT) and 2 (5.6%) were papillary serous carcinomas (Fig. 1). The age range of patients with MMRd tumors was 43–81 years, with a median age of 60 years. Tumor size ranged from 0.9–16 cm, with an average size of 5.5 cm. Lower uterine segment involvement was observed in 21 out of 36 cases (58.3%). Histopathologically, low-grade differentiation (Figs. 1,2), was observed in 24 cases (66.6%) similar to lymphoepithelial pattern which was present in 30 cases (83.3%). Myometrial involvement, exceeding half of the myometrium, was seen in 14 cases (38.9%). Focal clear cell components were observed in only one case (2.8%). Immunohistochemical analysis revealed paired loss of MLH1 and PMS2 in 31 cases (86.1%) and loss of MSH2 and MSH6 in 5 cases (13.9%). An example is illustrated in Fig. 2. Furthermore, two patients (5.6%) had a familial history of cancer. ER/PR positivity was observed in 11 cases (30.6%), while wild type p53 staining was seen in 28 cases (77.8%). Nodal metastasis was documented in 5 cases (13.8%). Overall, 12 cases (33%) exhibited a dismal prognosis based on clinical follow-up data. They were MLH1/PMS2 (12/12, 100%) deficient with aberrant p53 expression in half of them (6/12, 50%). Of note, none of the MMRd cases carried a mutation in *POLE* gene (Exomes 9, 13 and 14) (Table 1).

The significance of the p-values associated with each factor in (Table 2) was evaluated to determine the statistical significance of the relationship between MMRd and the factors analyzed. A p-value threshold of 0.05 was used to determine statistical significance. The analysis revealed that there was no

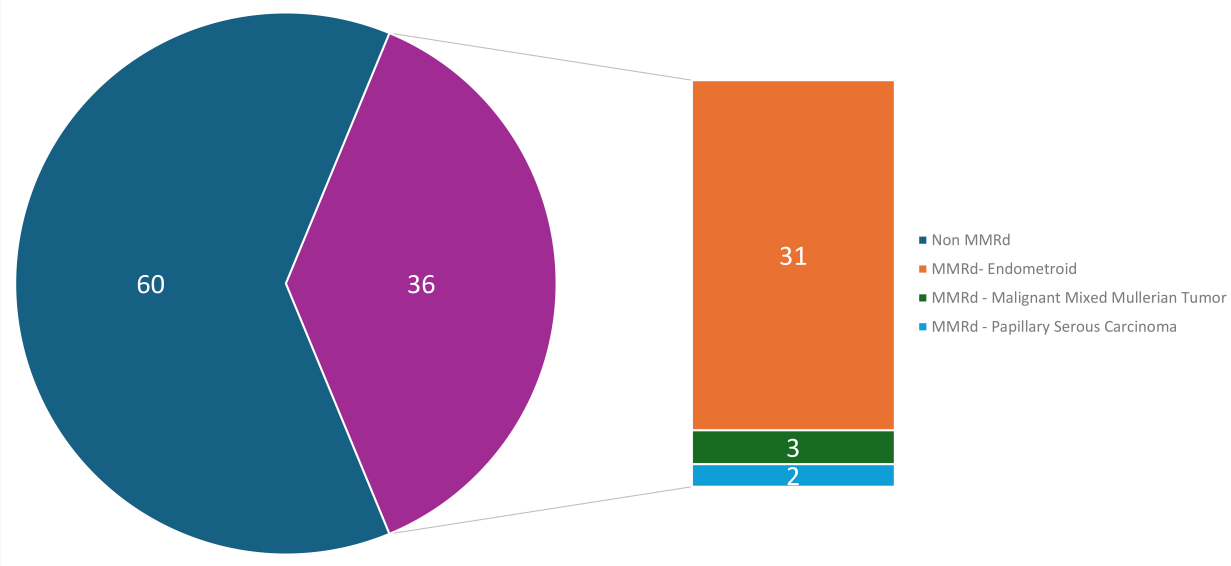

FIGURE 1. Breakdown of MMRd status across different subtypes. MMRd: Mismatch repair deficient.

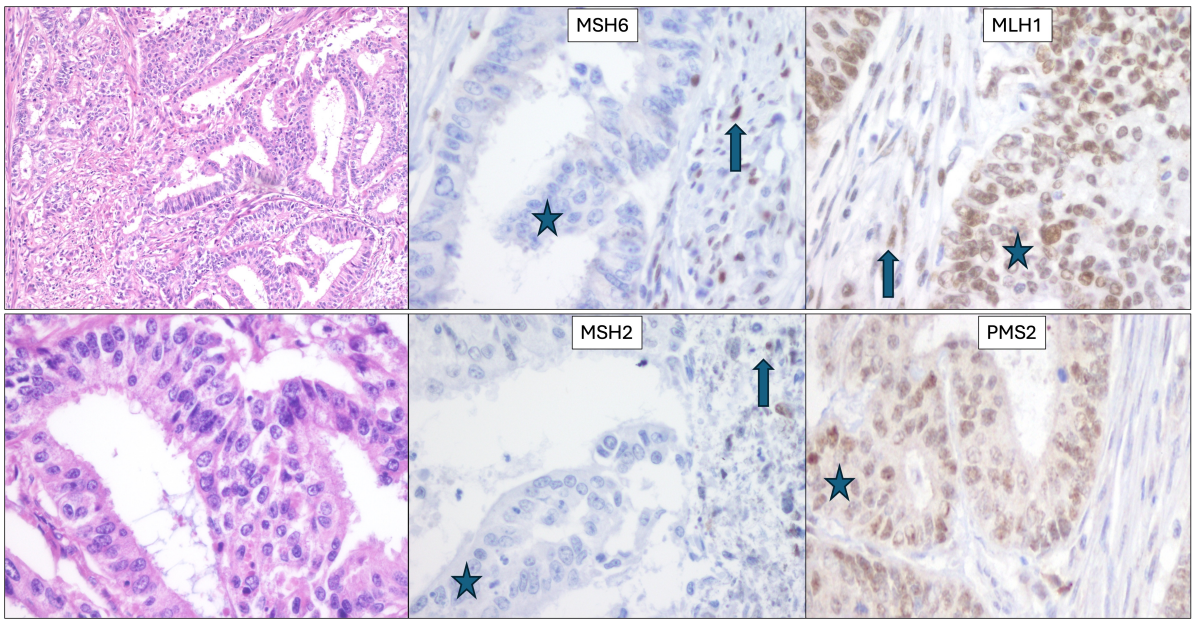

FIGURE 2. H&E example of endometrioid adenocarcinoma showing confluent glandular pattern with scant intervening stroma. On high power (40×), crowding malignant nuclei appear to be rounded with vesicular nuclei and prominent nucleoli. MMR markers immunostaining demonstrated retained expression of MLH1/PMS2 with absent nuclear staining of MSH2/MSH6 (star). Smooth muscle and lymphocytes serve as internal control (arrow head).

statistically significant association between MMRd and lower uterine segment involvement (p = 0.093), low-grade differentiation (FIGO 1–2) (p = 0.352), status of node metastasis (p = 0.635), myometrial involvement (p = 0.475), familial history of cancer (p = 0.983) or dismal prognosis (p = 0.891). However, a statistically significant association was observed between MMRd and the lymphoepithelial pattern (p = 0.014). These findings suggest that MMRd show a significant association with the lymphoepithelial pattern.

4. Discussion

In the evolving landscape of endometrial carcinoma research, recent studies have significantly contributed to our understanding of the prevalence and clinical impact of MMRd endometrial carcinoma.

A pivotal study by Sushmita *et al.* [14] (2020) analyzed the clinicopathologic features of endometrial cancer in various patient groups based on mismatch repair status and Lynch syndrome. The review, spanning 1990–2018, incorporated 29 studies with a total of 7057 endometrial cancer cases. The findings indicates that younger patients tend to have Lynch syndrome and MMRd tumors, in contrast to older patients who have tumors with intact mismatch repair and positive MLH1 methylation. Furthermore, it is less common for those with MMRd tumors to be diagnosed at the earliest stage of the disease. Notably, the profile of endometrial cancer patients with MMRd tumors shares similarities with those possessing

TABLE 1. Number of endometrial cases and pathological parameters evaluated.

Parameter	Number of Cases	Percentage
Total Cases Analyzed	96	-
MMRd Cases	36	37.5%
- Endometrioid Subtype	31	86.1%
- Mixed Mullerian Tumors (MMMT)	3	8.3%
- Papillary Serous Carcinomas	2	5.6%
Lower Uterine Segment Involvement	21	58.3%
Low-grade Differentiation (FIGO 1–2)	24	66.6%
Status of node metastasis	5	13.8%
Lymphoepithelial Pattern	30	83.3%
Myometrial Involvement	14	38.9%
Focal Clear Cell Components	1	2.8%
Loss of MLH1 and PMS2	31	86.1%
Loss of MSH2 and MSH6	5	13.9%
Patients with Familial History of Cancer	2	5.6%
ER/PR Positivity	11	30.6%
Wild Type p53 Staining	28	77.8%
Cases with Dismal Prognosis	12	33.0%

MMRd: Mismatch repair deficient.

TABLE 2. Analysis of MMRd in relation to various factors.

	MMRd		
	Number of cases	Percentage	*p*-Value
Lower uterine segment involvement	21	60.00%	0.093
Low-grade Differentiation (FIGO 1–2)	24	68.57%	0.352
Status of node metastasis	5	14.28%	0.635
Myometrial involvement	14	40.00%	0.475
Lymphoepithelial pattern	30	85.71%	0.014
Family history of cancer	2	5.71%	0.983
Dismal prognosis	11	31.42%	0.891

MMRd: Mismatch repair deficient.

hereditary mutations associated with Lynch syndrome, including factors such as their age, tumor grade, tissue histology and the stage of cancer development [14].

Atjimakul *et al.* [15] (2022) contributed to this domain by assessing the prevalence and impact of MSI-H in Thai patients with endometrial cancer. Their findings indicated that a notable proportion (24.5%) of these patients exhibited MSI-high status. Importantly, the study highlighted the association of MSI-high status with improved oncological outcomes, as evidenced by higher 3-year disease-free survival (DFS) and overall survival rates compared to the MSI-stable group. This study provides valuable epidemiological data on microsatellite instability in endometrial cancer within the Thai population and its implications for patient outcomes [15].

Mircea Guina's (2022) research offered a distinct perspective by focusing on MLH1 promoter hypermethylated (MLH1ph) endometrial cancers. The study found that patients with MLH1ph endometrial cancers exhibited unique molecular and clinical profiles, characterized by older age, obesity, advanced disease at diagnosis, lower tumor mutational burden and tumor-infiltrating lymphocyte scores [16].

Further contributing to the understanding of MMR deficiencies in endometrial carcinoma, Jain *et al.* [17] (2021) and Rekhi *et al.* [18] (2020) provided valuable insights into the prevalence and histopathological features of these cancers. Jain *et al.* [17] reported that 33% of their cases were MMRd, with the most common histologic tumor type being endometrioid adenocarcinoma (70%) similar to our findings. This study's significance lies in its detailed breakdown of MMR protein loss expression, highlighting MLH1/PMS2 loss as the most frequent. Rekhi *et al.* [18] found that among 104 endometrial carcinoma cases, nearly half (48%) were MMRd. Their research delved into the histopathological nuances, revealing that all cases were endometrioid adenocarcinomas of

varying FIGO grades and exhibited a range of molecular patterns in MMR protein loss [17, 18].

On national level, Bu *et al.* [19] (2022) conducted a study to ascertain the frequency of Lynch Syndrome among endometrial cancer patients in Saudi Arabia. 53 cases out of 436 (12.2%) exhibited MMR deficiency. MLH1 promoter hypermethylation was present in 30 cases (6.9%). Lynch syndrome was identified in three patients (0.7%): two with variants in the MSH2 gene and one in the MSH6 gene. Another three cases (0.7%) were categorized as having Lynch-like syndrome due to the presence of double somatic MSH2 pathogenic or likely pathogenic variants. These findings suggest that the prevalence of Lynch syndrome among endometrial carcinoma patients in Saudi Arabia is relatively low [19].

Consistent with previous literature, in our study, we found that MMRd tumors predominantly belonged to the endometrioid subtype as it constitutes the most common histotype, accounting for approximately 75–80% of cases [20]. It has a relatively high prevalence of MMRd, ranging from 17% to 20% [21, 22].

Serous carcinoma, a high-grade histological type of endometrial carcinoma, is less commonly associated with MMRd compared to endometrioid carcinoma. The prevalence of MMRd in serous carcinoma is estimated to be around 3.6–16% [23–25]. Serous carcinomas often exhibit other genetic alterations, such as TP53 mutations or ERBB2 gene amplification [26].

Clear cell carcinoma, characterized by clear cytoplasm and glycogen-rich cells, is another histological type of endometrial carcinoma. Two studies reported 11.3 and 19% of MMRd prevalence in clear cell carcinoma [27, 28]. Clear cell carcinomas frequently harbor other molecular alterations, including mutations in the ARID1A gene [29].

Mucinous carcinoma is a rare histological type of endometrial carcinoma, and limited data are available regarding the prevalence of MMRd in this subtype as it was not directly addressed in the recent literature.

In line with other research findings, our study noted the absence of expression in a dimer formation, specifically highlighting the frequent loss of MLH1 and PMS2 proteins. This loss emphasizes the role of the MLH1-PMS2 mismatch repair (MMR) complex in the pathogenesis of MMRd tumors [30]. Additionally, the discovery of a family history of cancer in some subjects underscores the hereditary aspects of MMRd tumors, suggesting the necessity for screening for related cancers in these individuals.

MMRd tumors exhibit certain features, such as ER/PR positivity, wild type p53 staining, and a lymphoepithelial pattern, which may influence therapeutic approaches [31]. The clinical significance of MSI in the treatment of endometrial carcinoma is imperative for advancing patient care. MMRd endometrial carcinomas respond favorably to immune checkpoint inhibitors like pembrolizumab due to their high mutational load, which produces neoantigens detectable by the immune system. These inhibitors activate the immune response to attack the tumors, which has been shown to shrink tumors and enhance patient outcomes [32, 33]. Despite the promise of immune checkpoint inhibitors, chemotherapy remains a cornerstone of treatment for MMRd endometrial carcinoma. Platinum-based regimens, including carboplatin and paclitaxel, are widely used across various microsatellite statuses [34]. Furthermore, there is a growing body of evidence supporting the use of targeted treatments, particularly PARP inhibitors, which leverage the DNA repair deficiencies inherent to MMRd to induce cell death [35, 36].

Our research also indicates a lower occurrence of high-grade differentiation in MMRd tumors, hinting at a correlation with more favorable clinical and pathological outcomes. The MMRd status is linked to a better prognosis in endometrial carcinoma [37, 38]. This prognosis is reflected in patients with MMRd tumors typically presenting with a lower stage of the disease, decreased lymph node involvement and improved overall survival in comparison to patients with MMR-proficient tumors [39, 40].

In our study, the observed lower prevalence of high-grade differentiation in MMRd tumors suggests their association with favorable clinicopathological features. MMRd status has been associated with good prognosis in endometrial carcinoma. Patients with MMRd tumors tend to have lower tumor stage, lower rates of lymph node involvement and better overall survival compared to those with MMR-proficient tumors [41].

Generally, MMRd status may be indicative of an underlying germline mutation, such as Lynch syndrome. Identifying patients with germline mutations has important implications for genetic counseling and screening of both the patient and their family members. It allows for early detection, prevention and management of associated cancers [42].

There are two major limitations in this research that could be addressed in future research. First, the retrospective nature of this study could introduce selection and data collection biases. Second, the absence of long-term follow-up data and potential unaccounted confounders are also concerns. For future research, it would be beneficial to conduct prospective, multicenter studies with larger and more diverse cohorts to validate the findings. Investigating the molecular mechanisms underlying MMR deficiency in greater detail and exploring targeted therapies for MMRd tumors could provide further insights. Studies focusing on the long-term outcomes of patients with MMRd tumors and the effectiveness of different treatment modalities are also needed to enhance patient care.

It's important to note that treatment decisions should be individualized based on factors such as tumor stage, grade, comorbidities and patient preferences. Multidisciplinary discussions involving medical oncologists, gynecologic oncologists, genetic counselors and other specialists are crucial for developing personalized treatment plans for patients with MSI endometrial carcinoma. Ongoing research and clinical trials are continuously exploring novel therapeutic approaches and refining treatment strategies for this specific molecular subtype of endometrial carcinoma.

5. Conclusions

The evaluation of MMR proteins in endometrial carcinoma allows for the identification of MMRd tumors, which exhibit distinct clinicopathological characteristics and prognostic implications. Our findings highlight the predominance of

endometrioid subtype, low-grade differentiation, significant myometrial involvement and the loss of specific MMR proteins in MMRd tumors similar to large number of studies in the literature. The association of ER/PR positivity and wild type p53 staining suggests potential therapeutic avenues for MMRd tumors. Furthermore, the observation of familial cancer history emphasizes the importance of appropriate genetic counseling and screening in affected individuals. Overall, the evaluation of MMR proteins in endometrial carcinoma contributes to a better understanding of this disease and may guide personalized treatment approaches in the future. Further research is needed to elucidate the underlying mechanisms and validate the prognostic significance of MMR status in a larger cohort.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

SS and FA—designed the research study, performed the research, analyzed the data, wrote the manuscript, read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Unit of Biomedical Ethics, Research Ethics Committee at King Abdulaziz University, Faculty of Medicine gave its approval (Reference No. 632-22) for the acquisition of archived tissue blocks.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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