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Study of Immunohistochemical Expression Patterns of Mismatch Repair Proteins in Endometrial Carcinoma and Endometrial Hyperplasia: An Institutional Study

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Abstract

Introduction Endometrial carcinoma (EC) is the most common cancer in women (7% of all malignancies) standing fourth in prevalence. Its molecular categorization has lately gained substantial importance, because of its prognostic implications and association of mismatch repair (MMR) proteins with Lynch syndrome.

Objectives Our aim of the study was to analyze the expression of MMR proteins (MLH1, PMS2, MSH6, MSH2) in EC and Endometrial hyperplasia (EH).

Materials and Methods This study was performed on 52 EC and 65 EH cases (7 cases - disordered proliferative endometrium, 12 cases - EH with atypia, 46 cases - EH without atypia). Immunohistochemical staining with MLH1, PMS2, MSH6, and MSH2 were performed. SSPS software version 25 with chi-square test was used in statistical analysis.

Results Out of 52 cases of EC, 42 (80.76%) cases were identified as MMRd.MLH1 negative expression, which was significant (*p*: 0.005) compared with other markers. Also, there was significant statistical correlation (*p*: 0.004) between lower International Federation of Gynecology and Obstetrics grade and MLH1/PMS2 loss. Only six cases of EC had notable family history. Of 12 cases of EH with atypia, 91.66% (11/12) were MMR deficient (MMRd), whereas in EH without atypia 69.23% (32/46) were of MMRd. Paired expression of MLH1/PMS2 and MSH2/MSH6 was observed in EC whereas it was not seen in EH. MLH1 loss was the most common protein loss both in EC and EH with atypia.

Conclusion MLH1/PMS2 combination was the most common protein deficiency seen in EC. We found considerable proportion of EC cases with MMRd. This implies the need of incorporating routine MMR protein assessment by immunohistochemistry in all the patients diagnosed as EC as it will affect the further treatment and management.

Keywords
- endometrial
- carcinoma
- hyperplasia
- MMR
- MLH1

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Introduction

With 417,000 new cases and 97,000 fatalities from uterine corpus cancer in 2020, it is the sixth most prevalent malignancy in women in India. Uterine cancer is the fourth most frequent cancer in women worldwide and the fifth largest cause of cancer deaths in the United States.[1–3] Lynch syndrome (LS) is an autosomal dominant genetic disease brought on by germline pathogenic variants in the mismatch repair (MMR) genes. LS are divided into Lynch type I and Lynch type II based on the sites. Lynch type I occurs in the colon or rectum and Lynch type II tumors occur in extraintestinal sites such as the endometrium, ovary, breast, urinary tract, stomach, hepatobiliary tract, small bowel, and brain.[4,5]

Deoxyribonucleic acid (DNA) MMR protein deficiency (MMRd) is an important mechanism of genomic instability in human cancers. It is seen in 20 to 43% of sporadic endometrial carcinomas (ECs) and in 75% of the EC associated with LS.[5] The essential participants in the MMR pathway, which has been widely explored, are MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, and PMS2 (MutL and MutS homologs).[2]

Endometrial hyperplasia (EH) is an uncontrollable growth of the endometrial glands that elevates the ratio of the glands to the stroma.[6,7] Depending on the degree of architectural irregularity and whether or not there is nuclear atypia, EH has been further divided in to (1) EH without atypia and (2) atypical EH/endometrial intraepithelial neoplasia (EIN).[7,8] EH without atypia results from prolonged estrogen exposure and progression to EC can happen in 1 to 3% of women. Atypical EH/EIN often arises as a localized clonal process in a background of EH without atypia. About 25 to 33% of women diagnosed as atypical EH/EIN will have cancer either at immediate hysterectomy or during the 1-year follow-up.[9]

Loss of MLH1 or MSH2 protein can be a precursor event in carcinogenesis of EC.[10] Some studies have found out that loss of MMR protein expression was higher in EH cases, which were either coexisting with EC or progressed to EC on follow-up.[11] Esteller et al also observed that aberrant MLH1 methylation is exclusively detected in atypical EHs.[12] Loss of MMR protein expression has been identified in the normal nonneoplastic crypts of colon in LS patients.[13] Similarly, loss of MMR protein expression in nonneoplastic endometrial glands was observed in 70% of patients with LS in another study suggesting the usefulness of MMR testing as screening tool in suspected LS patients.[14] These reports highlight the significance of testing for MMR protein loss in EH.

Microsatellite instability (MSI) testing or immunohistochemistry (IHC) for the MMR proteins can both be used to detect MMRd. The two techniques exhibit approximately 96% concordance and similar sensitivity. MMR IHC only determines whether the four MMR proteins are present or absent in cancer cells. The advantages of MMR IHC include lower costs, simple pathologist accessibility, suitability for IHC external quality assurance schemes, correlation with morphology, and identification of the faulty protein, which can then direct further testing. For MSI testing, there are several authorized commercial platforms available. This test is currently more expensive than IHC. DNA taken from tumor tissue is used for MSI testing.[2,15,16]

Previous studies on MMR deficiency in EC documented in the literature are mostly from developed countries. So, the present study is undertaken to evaluate the IHC expression of four MMR markers (MLH1, PMS2, MSH6, MSH2) in EC and EHs in histopathology samples received in a tertiary care hospital from the costal part of Southern India. Expression pattern of individual markers with respect to various clinicopathological parameters including grading and staging will be studied in ECs.

Materials and Methods

Study Design

This is a cross-sectional study of cases collected over 6 years (4years of prospective and 2 years of retrospective) from January 2016 to April 2022.

Sample Size

A total of 52 cases of EC and 64 cases of EH collected during the above study duration formed the sample cases of the study.

Medical reports of the patients were reviewed. All slides were reviewed by two pathologists with clinical details and histopathological details. The representative tissue blocks were selected for IHC. IHC with MLH1, PMS2, MSH2, and MSH6 of mouse antibody was performed. We used the Diagnostic BioSystem kit (6616 Owens Dr, Pleasanton, CA, United States) for all experiments. The details of each IHC markers are described in ►**Table 1**.

Primary and Secondary Outcome

Detecting the MMR protein deficiency in patients with EC and EH. Understanding the correlation between MMR protein deficiency in EC and pathological features, such as tumor grade, stage, tumor infiltrating lymphocytes (TILs), etc.

Inclusion and Exclusion Criteria

All cases of EC (resection samples) and sample cases of EH diagnosed during the study duration are included in the study.

Biopsy cases of EC were excluded. Improperly fixed specimen and blocks with scant tissue were also excluded.

Analysis of MMR Markers on IHC

Normal tonsil tissue was used as external negative (MMR intact) control. Colonic adenocarcinoma was used as positive control (MMRd). Loss of nuclear expression of at least one protein out of four was taken as MMRd otherwise the tumor was considered MMR proficient[17] (MMRp). Complete absence of staining in the tumor cells with positive staining of internal control cells (lymphocytes, stromal cells) and external control was considered as loss of expression of MMR markers. Presence of nuclear staining in tumor cells of any degree (weak to strong) to any extent (focal to diffuse) with positive internal and external controls was considered as positive staining for MMR markers.

Table 1 Describing details of IHC marker with clone, species, isotype, concentration, etc.

Immunogen	Clone	Species	Isotype	Concentration dilution	Pretreatment	Incubation time and temperature
Full length recombinant MLH1	G168–15	Mouse	IgG1	1:25–1:50	EDTA buffer pH 8.0	60 min at room temperature
Recombinant human PMS2	A16–4	Mouse	IgG1,k	Prediluted	EDTA buffer pH 8.0	30 min at room temperature
Recombinant fragment of MSH2 protein	DBM15.82	Mouse	IgG1,kappa	1:50–1:100	Tris-EDTA buffer pH 9.0	30 min at room temperature
Human MSH6	44	Mouse	IgG1	1:25–1:50	Tris-EDTA buffer pH 9.0	60 min at room temperature

Abbreviations: EDTA, ethylenediaminetetraacetic acid; IgG, immunoglobulin G; IHC, immunohistochemistry; MLH1, MutL homolog1; MSH2, MutS homolog2; MSH6, MutS homolog6; PMS2, PMS1 homolog2.

Statistical Analysis

IBM SSPS version 25 software version was used and calculated with chi-square analysis. Significance of loss of expression of MMRd markers and association of loss of expression of MMR markers with clinicopathological parameters such as tumor grade, stage, myometrial invasion, etc. were analyzed. A *p*-value of < 0.05 was considered significant for all analyses.

Ethical Approval

Study was approved by the institutional ethical committee (IEC KMC MLR 12–2020/449). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

A total of 52 ECs were studied for expression of MMR markers. Out of 52 cases of EC, 42 (80.76%) cases were identified as MMRd and 10 (19.23%) cases as MMRp on IHC. Clinicopathological features of ECs in MMRd and MMRp cases are depicted in ►**Table 2**. Of 65 sample cases of EH, 70.76% (46/65) cases were EH without atypia, 18.46% (12/65) cases were EH with atypia, and 10.76% (7/65) cases were disordered proliferative endometrium (DPE). Out of 46 cases of EH without atypia, 69.23% (32/46) were MMRd and 21.53% (14/46) were MMRp, whereas out of 12 cases of EH with atypia 91.6% (11/12) cases were MMRd, of 7 cases of DPE 9.23% (5/7) cases were MMRd, and 1.53% (2/7) cases were MMRp.

Clinical Features of EC Cases in Relation to MMR Status (►Table 2)

The age of EC patients in our study ranged from 39 to 79 years with a mean age of 59 years. Maximum number of cases in MMRd was seen in the 51 to 70 years age group, whereas in MMRp it was 41 to 60 years with a mean age in MMRd and MMRp being 59 and 52.5 years, respectively (*p*: 0.269). Out of 52 cases, majority of cases (60.8% [32/52]) were postmenopausal whereas 39.2% (20/52) were premenopausal. In MMRd cases postmenopausal women were 64.28% (27/42) and premenopausal were 35.71% (15/42), whereas in MMRp premenopausal and postmenopausal women were equal in number, that is, 50% (5/10) each (*p*: 0.420). Family history was traceable for 51.9% (27/52) cases. In those, six cases had notable family history. Out of six cases, 33.33% (2/6) had colorectal cancer followed by one case each of gastric, ovarian, endometrial, and breast cancer, and all these cases were MMRd on IHC (*p*: 0.538). In our study out of 42 cases of MMRd, body mass index (BMI) of 25 to 30 kg/m^2 was observed in 54.76% (23/42) cases of EC. Cases with BMI of 31 to 35 kg/m^2 were 42.85% (18/42), while BMI of 36 to 40 kg/m^2 were 9.52% (4/42). One case had (2.38% [1/42]) BMI of > 40 kg/m^2 (0.707). Out of 52 cases of EC 39% (19/52) were diabetic and 17.30% (9/52) were hypertensive and were on medication (*p*: 0.707).

Pathological Features

Out of 52 cases, majority were endometrioid EC (EEC) (96.15%, 50/52) followed by one case of clear cell carcinoma (1.92%, 1/52) and one case of mixed Mullerian tumor (1.92%,1/52). Myometrial invasion of more than 50% was seen in 33.33% (14/42) MMRd cases as compared with 20% (2/10) of MMRp cases (*p*: 0.520).

We graded according to the International Federation of Gynecology and Obstetrics (FIGO) grading system and found 90 0.38% (47/52) of cases to be grade I (►**Fig. 1A**), grade II had 2 (3.854%) cases, and grade III had 3 (5.78%) cases. There was significant correlation between MMR deficiency status and lower FIGO grade (*p*: 0.004). According to the TNM staging majority of the cases were diagnosed as stage T1a, 71.15% (37/52), in that 78.37% (29/37) cases were MMRd and 21.62% (8/37) were MMRp. StageT1b had 21.15% (11/52). In that 90.90% (10/11) cases were MMRd and 9.09% (1/11) cases were MMRp, whereas stage T3a had 5.76% (3/52), in that 66.66% (⅔) cases were MMRd and 33.33% (⅓) was MMRp. StageT2 being 1.59% (1/52) and was MMRd (*p*: 0.952).

Out of 52 cases, 13.7% (7/52) cases had lower uterine segment (LUS) involvement and all were MMRd. Cervical stromal involvement was seen in 5.77% (3/52) cases and all were MMRd (0.335). TILs were studied, which showed

Table 2 Clinicopathological features in EC in relation to MMR status

Variable	Category	*N* (%) *N*: 52	MMRd (*N*: 42) *N* (%)	MMRp (*N*: 10) *N* (%)	*p*-Value
Age in years	> 50	32 (61.53)	28 (66.66)	5 (50)	0.269
	< 50	20 (38.46)	14 (33.33)	5 (50)	
Menopausal Status	Premenopausal	20 (38.46)	15 (35.71)	5 (50)	0.420
	Postmenopausal	32 (61.53)	27 (64.28)	5 (50)	
Family History	Present	27 (51.92)	24 (57.14)	3 (30)	0.538
	Absent	25 (48.08)	18 (42.87)	7 (70)	
Histological type	EEC	50 (96.15)	41 (97.61)	9 (90)	**0.005**
	CCC	1 (1.92)	0	1 (10)	
	MMT[a]	1 (1.92)	1 (2.39)	0	
FIGO grade	Low grade (I)	47 (90.38)	39 (92.85)	8 (80)	**0.004**
	High grade (II and III)	II: 2 (3.84) and III: 3 (5.78)	3 (7.15)	2 (20)	
T stage	T1a	37 (71.15)	29 (69.04)	8 (80)	0.952
	T1b	11 (21.5)	10 (23.80)	1 (10)	
	T3a	3 (5.76)	2 (4.76)	1 (10)	
	T2	1 (1.59)	1 (2.4)	0	
Myometrium invasion	< 50%	36 (69.23)	28 (66.66)	8 (80)	0.520
	> 50%	16 (30.77)	14 (33.34)	2 (20)	
LUS involvement	Present	7 (13.47)	7 (16.66)	0	0.333
	Absent	45 (86.53)	35 (83.34)	10 (100)	
TILs	Present	32 (61.53)	26 (61.90)	6(60)	0.524
	Absent	20 (38.47)	16(38.1)	4 (40)	

Abbreviations: CCC, clear cell carcinoma; EC, endometrial carcinoma; EEC, endometrial endometrioid carcinoma; FIGO, International Federation of Gynecology and obstetrics; LUS, lower uterine segment; MMRd, mismatch repair protein deficient; MMRp, mismatch repair protein proficient; MMR, mismatch repair protein; MMT, mixed Mullerian tumor; T, tumor; TILs, tumor infiltrating lymphocytes.
[a]Mismatch repair protein proficient.
Note: The significant *p* values are bold faced.

61.53% (32/52) cases had TILs. Out of 42 MMRd cases TIL was seen in 81.25% (26/42) cases (*p*: 0.524) (►**Fig. 2D**).

IHC Expression of Individual Markers in EC and EH

Out of 52 EC cases, 80.76% (42/52) were MMRd (►**Fig. 2A–C**) and 19.27% (10/52) were MMRp (►**Fig. 1B–D**). Ten cases showed positive expression of all the four markers. The above findings are summarized in ►**Table 3**.

MLH1 and PMS2 were negatively expressed in all 80.7% (42/52) cases and PMS2 and MSH6 were negatively expressed in 26.93% (14/52) cases. Based on the negative expression in MMRd cases, MLH1 was the most important marker identified among the four markers (*p*: 0.005) (►**Table 3**).

Out of 12 cases of EH with atypia, 91.7% (11/12) cases showed loss of MLH1, which was followed by PMS2 (50.0%, 6/12), MSH6 (50.0%, 6/12), and MSH2 (8.3%, 1/12). Out of 46 cases of EH without atypia, MLH 1 was the most common marker to be lost (67.4%, 31/46) and this was followed by PMS 2 (34.8%, 16/46), MSH 6 (15.2%, 7/46), and MSH 2 (2.2%, 1/46). Of seven cases of DPE, MLH1 was the most common marker showing negative expression in 71.4% (5/7) cases. Negative expression of MSH2 was not seen in any of the cases (►**Table 4**)

Comparison of MMR Status in EC, EH with Atypia, EH without Atypia, and DPE

MLH1 was lost in 80.76% (42/52) cases of EC, 91.7% (11/12) cases of EH with atypia, 67.4% (31/46) cases of EH without atypia, and 71.4% (5/7) cases of DPE. With this we observed MLH1 to be the most common protein lost in both EC and EH compared with the other three markers (►**Tables 3** and **4**). Paired loss of MLH1/PMS2 and MSH2/MSH6 was seen in all cases of EC but this combination expression was not observed in EH. Both MLH1 loss and paired MLH1/PMS2 loss were statistically significant in EC compared with EH.

Discussion

In present study, the mean age of patients of EC in MMRd was 59 years (39–79 years), which is in concordance with similar other studies.[18–21] MMRd ECs are related with unfavorable outcome in women of 40 years of age and younger.[22] In our study, out of 42 cases of MMRd, 76. 19% (32/42) were postmenopausal women compared with 23.80% (15/42) of premenopausal patients (*p*: 0.420). Similar findings were seen in studies by others.[17,18]

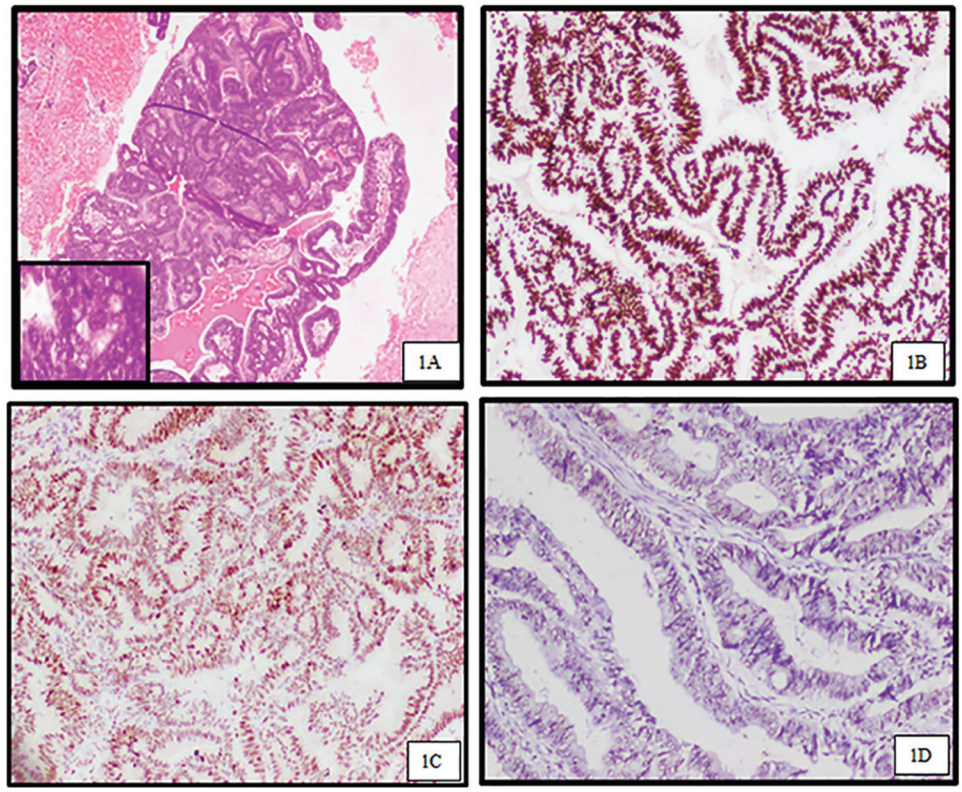

Fig. 1 (**A**) International Federation of Gynecology and Obstetrics (FIGO) grade 1 endometrioid endometrial carcinoma (EEC): complex glandular architecture with minimal intervening stroma (hematoxylin and eosin [H&E]: 10×), inset showing mild to moderate nuclear atypia (H&E: 40×). (**B**) MLH1 intact expression (10×), (**C**) MSH2 intact expression (10×), and (**D**) PMS2 focal intact expression (10×).

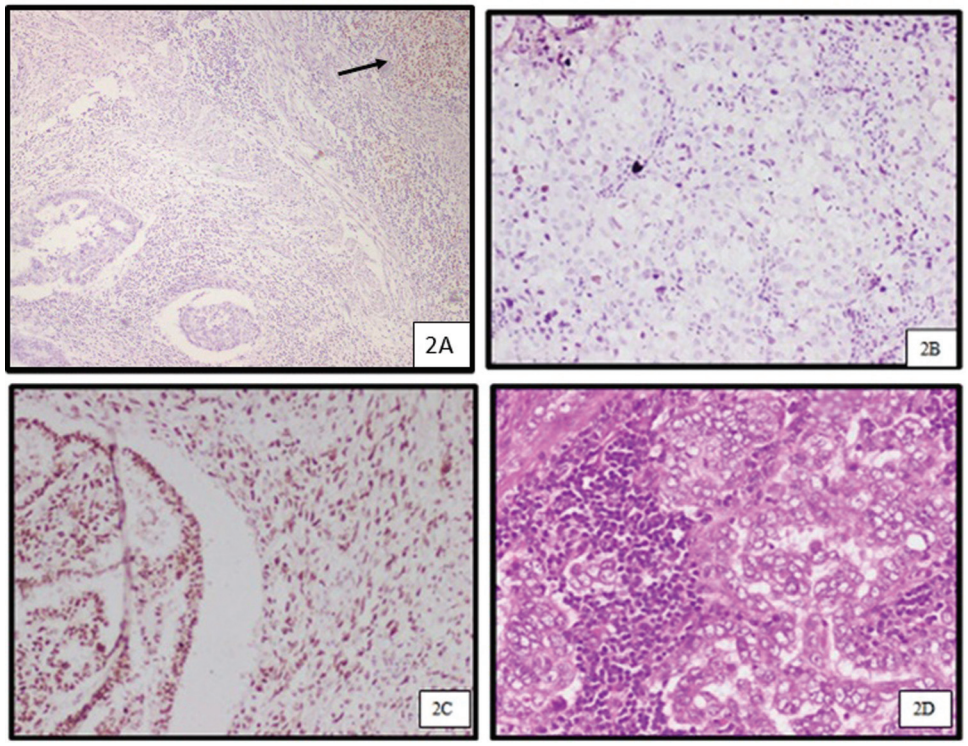

Fig. 2 (**A**) MLH1 protein loss in endometrioid endometrial carcinoma (arrow points the positively stained lymphocytes taken as internal control. 5×). (**B**) PMS2 protein loss in clear cell carcinoma (10×). (**C**) MSH2 intact expression in mixed Mullerian tumor (10×). (**D**) Tumor infiltrating lymphocytes surrounding tumor nests (hematoxylin and eosin [H&E]: 20×).

Table 3 IHC findings of individual markers in EC

N: 52	MLH1 *N* (%)	PMS2 *N* (%)	MSH2 *N* (%)	MSH6 *N* (%)
Negative	42 (80.77)	42 (80.77)	14 (26.93)	14 (26.93)
Positive	10 (19.23)	10 (19.23)	38 (73.07)	38 (73.07)
p-Value	**0.005**	0.0912	0.256	0.248

Abbreviations: EC, endometrial carcinoma; IHC, immunohistochemistry; MLH1, MutL homolog1; MSH2, MutS homolog2; MSH6, MutS homolog6; PMS2, PMS1 homolog2.
Note: The significant *p* values are bold faced.

Table 4 IHC findings of individual markers in EH

	EH with atypia (11/12)		*p*-Value	EH without atypia (31/46)		*p*-Value	DPE (5/7)		*p*-Value
	Negative	Positive		Negative	Positive		Negative	Positive	
MLH1	11 (91.7)	1 (8.3)	0.96	31 (67.4)	15 (32.6)	1.23	5 (71.4)	2(28.6)	0.235
PMS2	6 (50)	6 (50)	0.84	16 (35.8)	30 (65.2)	0.36	2 (28.6)	5(71.4)	0.852
MSH2	1 (8.3)	11 (91.7)	1.25	1 (2.2)	45 (97.8)	0.95	0	7(100.0)	0.006
MSH6	6 (50)	6 (50)	0.69	7 (15.2)	39 (84.8)	2.32	3 (42.9)	4(57.1)	0.952

Abbreviations: DPE, disordered proliferative endometrium; EH, endometrial hyperplasia; IHC, immunohistochemistry; MLH1, MutL homolog1; MSH2, MutS homolog2; MSH6, MutS homolog6; PMS2, PMS1 homolog2.

In the present study, six cases (out of 27 cases where family history was traceable) had notable family history of cancer in the first-degree relatives and all these cases were MMRd. In the studies conducted by Hashmi et al and Jain et al they observed a significant correlation between family history of cancers (43.8%, 7/16 and 29.62%, 8/27, respectively) and MMRd status, which is probably linked to the LS. They observed EC to be the most common cancer followed by colorectal carcinoma and pancreatobiliary cancers in the familial cancers.[18,20]

In our study, majority of cases were of lower FIGO grade and this was also reflected in MMRd cases (82.97%, 39/42) (*p*: 0.005). Study conducted by Jain et al, Sharma et al, and Doghri et al observed 66.66% (18/27), 63.2% (55/102), and 81.81% (36/44) cases, respectively, of MMRd in grade 1 and found statistically significant results for lower grade and MMRd status (0.51, 0.002, and 0.017, respectively).[5,19,20] We had majority of cases of EEC (97.61%, 41/42) (*p*: 0.005). Study conducted by Ramchander et al observed majority of cases in MMRd as EEC (88%, 29/33) and were statistically significant (0.01) in MMRd patients.[23]

In LS, LUS involvement is seen more frequently. These cases often show endometrioid histology, poorly differentiated, and show prominent TIL.[8] In the present study, LUS involvement was seen in 16.66% (7/42) cases of MMRd. Jain et al, Puangsricharoen et al, and Tangjitgamol et al observed 77.77% (21/27) cases, 64.9% (37/57) cases, and 87.5% (⅞) cases, respectively, of MMRd with LUS involvement and was statistically significant.[17,20,21]

In our study, out of 42 MMRd cases the majority (61.90%, 26/42) of cases showed TIL. However, it was not statistically significant (*p*: 0.524). Lacin et al, Bounous et al, and Chavez et al also observed that MMRd patient had increased TIL than MMR intact cases.[24–26] These studies stated that MMRd cases, which had increased TILs, will show very good immune response and they are likely to respond to immunotherapy.[26]

In this study, the combined loss of MLH1 and PMS2 was the most common abnormality detected in 75% (39/52) EC cases and 92.85% (39/42) of MMRd cases. Study conducted by Sharma et al, Hashmi et al, and Jain et al observed paired MLH1 and PMS2 loss in 50% (11/22), 60.71% (34/56), and 62.96% (17/27) of MMRd cases, respectively.[5,18,20] In the current study MSH2/MSH6 loss was seen in 26.92% (14/52) of EC and 33.33% (14/42) cases of MMRd. Hashmi et al and Ismael et al showed 3.3% (2/60) and 3.1% (4/56) cases of paired MSH2/MSH6 loss, respectively. They also observed that there was less common protein loss compared with MLH1/PMS2 similar to our study.[18,27] In contrast, in a study conducted by Fountzilas et al on MMR deficiency in colon and ECs MSH2 protein loss of 72.5% (58/80) was most common loss observed in EC, whereas PMS2 was the common protein loss in colon cancer.[28]

In our study, we did not find isolated loss of any of the four markers in EC. In EC, cases which showed MLH1 loss also showed loss of PMS2 and cases which had shown MSH2 loss also had MSH6 loss. In contrast, the study conducted by Mwafy et al showed isolated loss of MLH1 in 37.93% (11/80) cases.[29] Also, the study conducted by Jain et al showed isolated loss of PMS2 (2%, 2/27) and MSH2 (2%, 2/27).[12] Either MSH2 loss or MSH2 with MSH6 loss indicates mutation in MSH2. Loss of MLH1 either alone or combined with PMS2 suggests abnormality in MLH1, which can be a mutation or promoter methylation. There is heterodimer binding of MSH2 and MSH6 (or of MLH1 with PMS2), which is the basis for instability in the second protein if the first one is defective.[8,30]

Out of 65 cases of EH, 11 cases of EH with atypia (91.7%, 11/12) were MMRd. Lucas et al, Nieminen et al, and Han et al

observed 100% (8/8), 92% (11/12), and 70% (14/20) cases as MMRd in EH with atypia in their study.[6,31,32] In our study, 69.56% (32/46) cases of EH without atypia were MMRd. Other studies have showed variable results in EH without atypia cases. Studies conducted by Nieminen et al, Catena et al, and Raffone et al observed 100% (3/3), 50% (3/6), and 6.38% (3/47) cases, respectively, as MMRd in EH without atypia cases.[31,33,34] MMRd in EH may be a precursor event in endometrial carcinogenesis and identifying this will alert the clinician for follow-up of the patient. In those cases where there is suspicion of LS, genetic testing should be recommended.

Limitations

Of 52 cases more than 96.15% (50/52) cases were of EEC. We had very few cases of other histological types such as serous carcinoma and clear cell carcinoma for comparison.

Conclusion

Considerable proportion of EC cases were MMRd in our study. This implies the need of incorporating routine MMR protein assessment by IHC in all the patients diagnosed as EC as it will affect the further treatment and management. Testing for MMRd in EH cases also can be done in suspected LS cases as a screening test. More studies with large number of cases need to be done to explore the incidence of MMRd in the Indian population.

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Conflict of Interest
None declared.

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