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Loss of Mismatch Repair Protein Expression in Unselected Endometrial Adenocarcinoma Precursor Lesions

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Abstract

Objective—The benefit of evaluating the precursor of endometrial carcinoma, endometrial hyperplasia (intraepithelial neoplasia [EIN]), for loss of mismatch repair (MMR) protein expression and Lynch syndrome has yet to be determined. The present study aims to establish the incidence and type of loss of MMR protein expression in unselected premalignant lesions of endometrial adenocarcinoma, as well as the agreement of immunohistochemical staining in pretreatment endometrial biopsy (EMB) specimens with subsequent uterine resections.

Methods—A retrospective review identified 112 endometrial biopsies meeting criteria for endometrial EIN. Slides made from tissue microarray blocks were evaluated using antibodies against MLH1, PMS2, MSH2, and MSH6. Cases with a deficit in MLH1 were evaluated for gene promoter hypermethylation by polymerase chain reaction analysis. Fifty-four subsequent hysterectomy specimens were retrieved and assessed for MMR protein expression.

Results—Of the 112 endometrial biopsies with EIN, 4.5% (5/112) exhibited loss of MMR protein expression. The majority (4/5) demonstrated a deficit of MLH1, of which all exhibited inactivation via promoter hypermethylation. A single case displayed an absence of MSH6. Age was not significantly associated with MMR deficiency. There was no significant association between MMR status in the EMB and a subsequent diagnosis of cancer. Immunohistochemical staining in all successive hysterectomy cases was concordant with the pattern observed in the EMB specimen.

Conclusions—Sporadic hypermethylation of MLH1 seems to be the primary mechanism underlying defective MMR protein expression in EIN. Among our cohort, only 1 patient (<1%) had a mutation suggestive of a hereditary inheritance. Hence, the utility of evaluating EIN for MMR protein expression as a screen for Lynch syndrome is limited, regardless of age.

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The authors declare no conflicts of interest.

Keywords

Endometrial hyperplasia; Endometrial intraepithelial neoplasia; Mismatch repair; Lynch Syndrome

Endometrial cancers are generally classified as type 1 or type 2.¹ Type 1 cancers typically display endometrioid histology and often are associated with estrogen-driven precursor lesions. Type 2 cancers are typically of clear cell or serous histology and arise in a background of atrophic or inactive endometrium.^{2–4} The architectural and cytological criteria for type 1 precursors have been defined by Mutter et al,⁵ this premalignant lesion is termed endometrioid intraepithelial neoplasia (EIN). Although considerable research has been conducted to elucidate the genetic and bio-molecular changes associated with endometrial cancer,^{6–9} relatively little is known regarding the early evolution of these changes and whether significant alterations in gene function occur in the premalignant phase.

Alterations in mismatch repair (MMR) gene function are known to be associated with endometrial cancer.¹⁰ Defects in MMR involving the MLH1 (mutL homolog 1), PMS2 (PMS1 homolog 2), MSH2 (mutS homolog 2), and MSH6 (mutS homolog 6) genes may be due to germline mutations, known as Lynch syndrome.¹¹ Women with Lynch syndrome have a markedly increased risk of developing endometrial cancer.^{12–15} Defective MMR expression may also arise through an acquired inactivation of the MLH1 gene, associated with hypermethylation of the promoter region.¹⁶ Previous studies investigating the clinical and pathologic features of MMR defective endometrial cancer seem to suggest that this represents a unique subset of patients.^{17–19} Although many of these cancers present in younger women and often are endometrioid in histology, they seem to be associated with a poor or mixed prognosis.^{20–24} It is unclear, however, whether MMR defective endometrial cancers arise in association with a specific precursor lesion or are associated with EIN.

Although investigators have identified EIN and atypical hyperplasia in patients with Lynch syndrome,^{7,25–28} this seems to be a relatively uncommon event and the incidence of Lynch syndrome in patients with EIN remains unclear. It is also indefinite whether epigenetic defects due to sporadic MLH1 promoter region hypermethylation are associated with EIN and whether this plays a prominent role in early carcinogenesis. The current study, therefore, was undertaken to examine the incidence of loss of MMR protein expression in an unselected group of endometrial precursor lesions diagnosed by endometrial biopsy (EMB).

MATERIALS AND METHODS

This study was granted approval from the institutional review board. A retrospective review of the pathology database at the Queen's Medical Center (Honolulu, Hawaii) of all cases of complex endometrial hyperplasia in an EMB from January 7, 2009 to May 21, 2014 revealed 161 specimens. Hematoxylin and eosin–stained whole-slide sections were reviewed by a gynecologic pathologist (D.M.S.) using the criteria outlined by Mutter et al²⁹ for EIN, including architectural gland crowding, abnormal cytology, size greater than 1 mm, and

exclusion of carcinoma/mimics.³⁰ Of these, 69.6% (112/161) meet all 5 criteria for inclusion.

Formalin-fixed, paraffin-embedded tissue microarray (TMA) blocks were constructed from 2.0-mm representative areas of EIN. The TMA was evaluated for loss of nuclear staining after immunohistochemical (IHC) analysis with antibodies against MLH1, PMS2, MSH2, and MSH6. Before IHC staining, antigen retrieval was performed with EnVision FLEX Target Retrieval Solution, High pH (Dako, Carpinteria, Calif) at 97°C for 20 minutes. Mismatch repair protein expression was evaluated using antibodies to MLH1 (clone G168-15, 1:75 dilution, Biocare Medical, Concord, Calif), PMS2 (clone A16-4, 1:300 dilution, Biocare Medical), MSH6 (clone BC/44, 1:100 dilution, Biocare Medical), and MSH2 (clone FE11, 1:100 dilution, Biocare Medical) performed on 4-µm tissue sections. Detection was achieved using the MACH 3 Mouse HRP-Polymer Detection Kit (Biocare Medical). Diamniobenzidine (Dako) and hematoxylin (Dako) were used for chromogenic detection and counterstaining, respectively.

The immunohistochemistry specimens were deemed positive if any tumor nuclei demonstrated staining, with expression by adjacent lymphocytes and/or stromal cells considered a positive internal control. Results from 21 cases from the TMA were verified with whole-slide staining of tumor tissue. Cases with loss of MLH1 protein expression by IHC were further evaluated via a polymerase chain reaction–based assay performed on the formalin-fixed, paraffin-embedded tumor tissue for MLH1 promoter hypermethylation at a reference laboratory (Mayo Medical Laboratories, Rochester, Minn).

Upon review of the 112 endometrial biopsies demonstrating EIN, 54 had a subsequent hysterectomy specimen available for further analysis. These cases were retrieved and reviewed for the presence of EIN or carcinoma. Representative whole slide sections were selected for IHC staining with antibodies against MLH1, PMS2, MSH2, and MSH6 and processed via the previous procedure.

Statistical analyses were performed using the Wilcoxon rank sum test to compare age between the 2 groups as non-parametric approach and Fisher exact test to assess MMR expression and subsequent development of malignancy. Sensitivity and specificity were determined. Statistical significance was defined as a *P* value of less than 0.05.

RESULTS

Of the 112 endometrial biopsies demonstrating EIN, the mean age was 50.4 years. Loss of expression of MMR proteins was seen in 5 (4.5%) of 112 of EMBs. Of these, the majority (4/5) demonstrated defective expression of MLH1 (Table 1). A single case displayed an absence of MSH6. Age was not significantly associated with MMR deficiency (*P* = 0.92).

The clinicopathologic features of the 5 patients with loss of MMR protein expression are shown in Table 1. Three of the women with loss of MMR expression in the EMB underwent subsequent hysterectomy, all of which revealed carcinoma. The remaining 2 patients were lost to follow-up. The youngest patient in the cohort, 37 years old with loss of MLH1, also had the highest International Federation of Gynecology and Obstetrics stage (3C) at the time

of hysterectomy. A second 50-year-old patient was also of high stage (3A) and showed loss of expression of MLH1 in both the EMB and hysterectomy. The final patient with a subsequent hysterectomy also demonstrated a loss of MLH1; this patient was relatively older at the time of diagnosis (55 years) and presented at a lower stage. All patients with a deficit of MLH1 also exhibited MLH1 promoter hypermethylation by polymerase chain reaction. A single 43-year-old patient displayed loss of expression of MSH6 on EMB and was lost to follow-up.

Of the 54 patients with a subsequent hysterectomy specimen available for analysis, 55.6% (30/54) displayed carcinoma, whereas a single case revealed benign histology and the remaining 23 cases showed EIN. There was no significant association between MMR status in the EMB and a subsequent diagnosis of cancer ($P = 0.25$). Three cases exhibited loss of MMR protein staining in the successive hysterectomy, of which all were concordant with the staining pattern in the EMB specimen (sensitivity 100%). All cases with MMR protein expression retained in the uterus also demonstrated a lack of loss of expression in the EMB (specificity 100%).

CONCLUSIONS

Approximately half of women with Lynch syndrome present with a gynecologic malignancy as their “sentinel cancer.”¹⁵ Therefore, identification of Lynch syndrome–associated endometrial cancer in the premalignant phase may be potentially advantageous. Patients with a germline mutation and their family members would benefit from early treatment and appropriate genetic counseling.¹⁹ Currently, many institutions offer universal screening for all women with endometrial cancer, regardless of age or family history.^{31–33} Immunohistochemistry for MMR protein expression is an effective screening tool,³⁴ followed by germline testing as indicated.³⁵ Therefore, the current study was undertaken to assess the effectiveness of screening for Lynch syndrome in patients presenting with EIN on pretreatment biopsy.

The gastroenterology literature has examined the role of loss of MMR protein expression in adenomatous polyps, the premalignant lesion of colorectal carcinoma.^{36–41} Shia et al³⁶ suggested that evaluating adenomas with IHC might be productive in a clinically defined subset of patients, such as those with a strong family history of colorectal cancer. However, screening of unselected adenomas has not been shown to be an effective strategy for identifying novel cases of Lynch syndrome.^{37,38,41} Similarly, the current study found only 1 patient, less than 1% of patients with EIN, who demonstrated a pattern of MMR deficiency potentially associated with Lynch syndrome. Although loss of MMR protein expression has been observed in premalignant lesions in patients with Lynch syndrome,^{7,25–28} it seems to be a relatively infrequent event in an unselected population of patients with EIN. Therefore, IHC screening for Lynch syndrome in the setting of EIN does not seem to be warranted.

In unselected cases of EIN, the current study demonstrates 4.5% (5/112) of patients who exhibited a deficit in MMR protein expression. Four of these were associated with acquired hypermethylation of the MLH1 gene; of which, at least 3 were associated with cancer. Similarly, Sutter et al⁴² also noted that all cases of loss of MMR protein expression in

patients with complex atypical hyperplasia were associated with a concurrent invasive cancer. Presumably, the increased genetic instability associated with MMR loss translates into a more rapid evolution or progression to invasive cancer. Sporadic hypermethylation seems to be the primary mechanism underlying loss of MMR protein expression in EIN. In this cohort, all of the patients with MLH1 deficiency and a subsequent hysterectomy displayed carcinoma in the definitive specimen. The risk of invasive malignancy associated with MLH1 hypermethylation was not significantly different from the risk of malignancy with normal MMR expression. This was a relatively small number of patients and, however, further investigation in this area is warranted.

In the current study, there were 54 patients who underwent definitive surgery, 30 of which were found to have an invasive cancer upon hysterectomy. Loss of MMR protein expression was noted in 3 (10%) of these patients. This 10% rate of loss of expression in endometrial cancer patients is lower than the 21% to 35% reported in the literature^{32,43,44} and 19.6% previously reported in our population.⁴⁵ This suggests that MMR-associated endometrial cancer is more likely to arise de novo and may not be associated with EIN. Classic type 1 endometrial cancers and EIN are estrogen dependent and are associated with PTEN, ARID1A, and KRAS mutations. Type 2 endometrial cancers have been traditionally described as estrogen independent, higher grade, and associated with alterations in P53,^{4,46,47} although estrogenic factors may play a role in carcinogenesis.⁴⁸ The absence of a conventional estrogen-dependent precursor lesion in MMR-associated endometrial cancer seems to support observations that loss of MMR protein expression often correlates with the presence of poor or mixed prognostic features.^{20–24} It remains to be seen how precursor lesions such as EIN will be incorporated into the recent classification of endometrial carcinomas into 4 groups by the Cancer Genome Atlas Research Network.⁹

There are several limitations to this retrospective study. First, germline mutational analysis was not available for the single patient with loss of MSH6 expression. This patient was lost to follow-up. However, isolated loss of expression of MSH6 in endometrial carcinoma is frequently indicative of a Lynch syndrome-associated germline mutation.³⁵ Although this patient did not undergo subsequent confirmatory mutational analysis, there is a high likelihood that she carries a deleterious mutation consistent with Lynch syndrome. Second, risk factors such as a personal or family history of malignancy were not assessed. It is possible that as in adenomatous colorectal polyps, a certain subset of patients may benefit from MMR IHC screening.

In summary, within this unselected cohort of endometrial biopsies, the efficacy of evaluating EIN with MMR protein IHC as a screen for Lynch syndrome is limited. Only 1 patient in this series was found to have a pattern of MMR loss consistent with Lynch syndrome diagnosed on pretreatment biopsy. Although IHC evaluation of an EMB specimen for a subsequent deficit in protein expression in an ensuing hysterectomy is highly sensitive and specific, given the low-yield, screening women with EIN in an EMB for loss of MMR protein expression is an ineffective detection strategy. Hence, unselected screening of women with EIN for Lynch syndrome shows little utility.

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TABLE 1

Clinicopathologic Features of Patients With Loss of MMR Protein Expression in an EMB Displaying Endometrial EIN

Case	Age	MMR LOE	Subsequent Hysterectomy (dx)	MMR LOE in Hysterectomy	Grade	FIGO Stage	Additional Genetic Testing
1	37	MLH1	Yes (carcinoma)	MLH1	1	3C1	Hypermethylated
2	43	MSH6	No (lost to follow-up)	NA	NA	NA	NA
3	50	MLH1	Yes (carcinoma)	MLH1	2	3A	Hypermethylated
4	55	MLH1	Yes (carcinoma)	MLH1	1	1A	Hypermethylated
5	67	MLH1	No (lost to follow-up)	NA	NA	NA	Hypermethylated

Dx, diagnosis at hysterectomy; FIGO, International Federation of Gynecology and Obstetrics; LOE, loss of expression; NA, not applicable.