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Immunohistochemistry for mismatch repair protein deficiency in endometrioid endometrial carcinoma yields equivalent results when performed on endometrial biopsy/curettage or hysterectomy specimens

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HIGHLIGHTS

- Lynch syndrome screening can be accurately performed on endometrial carcinoma in biopsy and curettage specimens.
- Immunohistochemistry has equal accuracy on endometrial biopsy/curettage specimens and hysterectomy.
- Earlier Lynch syndrome screening may improve uptake of genetic counseling.

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ABSTRACT

Objective. Universal screening of endometrial cancer (EC) for Lynch syndrome (LS) has been increasingly implemented in the past five to ten years. Most pathologists initiate screening with immunohistochemistry (IHC) for mismatch repair proteins (MMRPs), using either pre-surgical samplings (endometrial biopsy or curettage, EMB/C) or hysterectomy specimens. We report a systematic assessment of the equivalence of IHC for LS screening on EMB/C versus hysterectomy specimens.

Methods. We identified 99 patients diagnosed with endometrioid EC and performed IHC for MMRPs MLH1, MSH2, MSH6, and PMS2 on their diagnostic EMB/C and paired hysterectomy specimen. Each specimen was scored as MMRP-retained or MMRP-deficient.

Results. Ninety-one EMB/Cs had carcinoma, while 8 EMB/Cs showed only complex atypical hyperplasia (CAH). Carcinoma was identified in all 99 hysterectomy specimens. Considering all 99 patients tested, concordance of MMRP expression pattern between EMB/C and paired hysterectomy specimen was 100%. Sixty-nine cases retained all four MMRPs, while 30 were MMRP deficient (26 MLH1- and PMS2-deficient, 3 MSH2- and MSH6-deficient, 1 PMS2-deficient).

Conclusions. In screening for LS in EC, IHC for MMRPs can be performed with identical accuracy on either EMB/C or hysterectomy specimens. Routine testing of diagnostic EMB/Cs may lead to earlier detection of MMRP deficiency, with improved patient uptake of genetic counseling and potential for earlier identification of immunotherapy candidates. Furthermore, reliable IHC-based LS screening performed on EMB/C can guide patient management and genetic counseling in patients unable to undergo hysterectomy.

1. Introduction

Lynch syndrome (LS) is a relatively common familial cancer syndrome, with an estimated population prevalence ranging from 0.3–5.8% [1]. Individuals with LS have increased risk of cancer of the colon, endometrium, stomach, ovary, brain, urinary tract, pancreatobiliary tract, and sebaceous glands [2]. Approximately 2–5% of endometrial carcinomas (EC) occur in the setting of LS, equaling or even exceeding the proportion of colorectal carcinomas (CRC) attributed to LS [3,4]. Women with LS are estimated to have a 29–33% lifetime risk for developing EC [2,5], and account for some 9% of EC diagnosed before age 50 [6]. Finally, more than half of women with LS present with EC as their sentinel malignancy [7], serving as a bellwether for identification of LS, and opening the door to appropriate screening and management of both the affected patient and her family members.

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Despite its relatively high population prevalence, targeted interventions to reduce risk in affected patients, and broad familial implications of this diagnosis, LS remains difficult to detect in patients. Physicians are uncomfortable with counseling patients on LS screening [8], and none of the clinicopathological screening tools introduced in the last three decades [9] has fully withstood rigorous scientific scrutiny [10–14] or optimally promoted proper genetic counseling and testing [15]. In this same time period, increasingly robust tools have become available for LS diagnosis, including immunohistochemical and molecular tumor screening tests and germline confirmatory studies. The broad availability of immunohistochemistry (IHC), in particular, has permitted both academic and community-based pathologists to institute universal LS screening protocols – first for CRC and, more recently, for EC (Fig. 1) [10,15–20], with emerging evidence for the cost-effectiveness of this approach [11].

However, despite (and perhaps because of) the rapidly expanding use of IHC for LS screening, testing protocols vary considerably between institutions [21]. In particular, some institutions screen pre-surgical diagnostic specimens (i.e., endometrial biopsy or curettage specimens, EMB/C), while others defer screening to the hysterectomy specimen. To date, the applicability of LS screening tools to EMB/C specimens has not been rigorously verified to determine the accuracy of this technique. All reports of single- and multi-institutional experience with universal LS screening of EC have included only hysterectomy material [10,15,16,19,22–24]. A single recent study reporting concordance of mismatch repair protein (MMRP) expression in EMB/C and hysterectomy specimens principally examines molecular classification of EC [25], with only brief allusion to potential utility in LS screening.

MMRP IHC testing on EMB/C specimens may offer the technical advantage of prompt and complete tissue fixation, compared with larger hysterectomy specimens, in which formalin fixation may be considerably delayed by surgery-pathology workflows and slow formalin penetrance of a bulky specimen. And from a clinical standpoint, knowledge of a positive MMRP screening on an EMB/C specimen may help to streamline care and increase timely uptake of genetic testing, as patients with early stage disease not requiring adjuvant therapy may not prioritize genetic testing after hysterectomy for EC. Knowledge of LS screening results prior to hysterectomy can also guide surgical planning and peri-operative counseling. For instance, in young women with EC, pre-surgical identification of LS could prompt discussion of lifetime risk for ovarian cancer associated with LS and significantly alter decisions on possible ovary-sparing surgery.

Here we report a systematic evaluation of MMRP expression in paired EMB/C and hysterectomy specimens from women diagnosed with EC at our institution, and discuss the implications for LS screening and management. We hypothesized that MMRP expression results would be non-inferior in the EMB/C specimen, compared to paired hysterectomy specimens.

2. Methods

We identified all EC cases with pure endometrioid or mixed endometrioid (including dedifferentiated) histology diagnosed between 2004 and 2016 in our institutional pathology database. This study was approved by our institutional IRB (#17–173) with waiver of

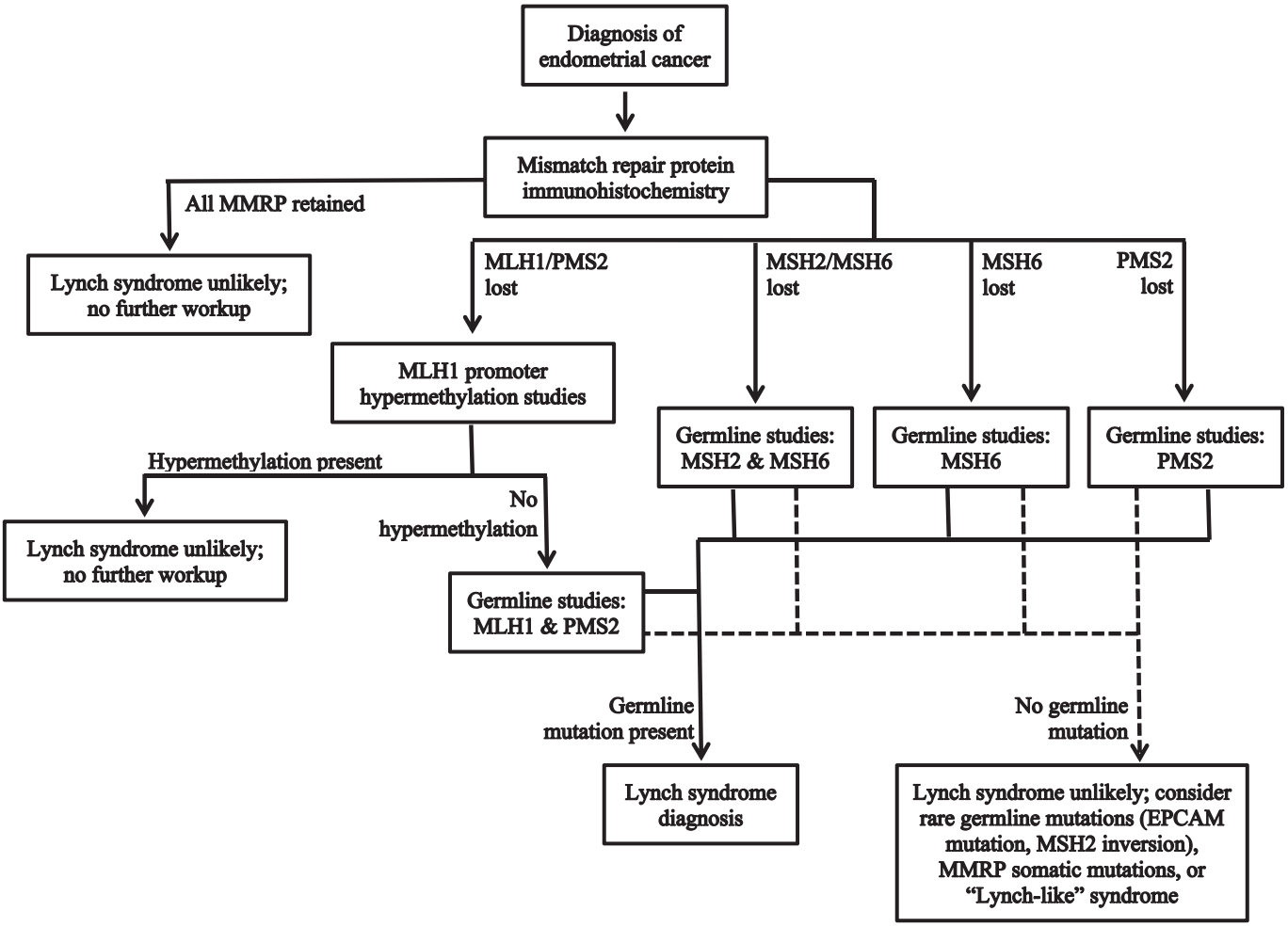

Fig. 1. Algorithm for universal Lynch syndrome screening and diagnosis [23].

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