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Impact of an immunohistochemistry-based universal screening protocol for Lynch syndrome in endometrial cancer on genetic counseling and testing☆

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HIGHLIGHTS

- Universal screening of endometrial cancer for Lynch syndrome using an immunohistochemistry-based protocol is feasible in a tertiary referral medical center.
- Triaging patients to genetic counseling based on immunohistochemistry screening results for Lynch syndrome is associated with higher patient follow-up.
- Universal screening of newly diagnosed endometrial cancer cases for Lynch syndrome leads to higher rates of germline genetic testing.

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ABSTRACT

Objective. Evaluate effects of a Lynch syndrome universal screening protocol in newly diagnosed endometrial cancers on subsequent genetic counseling (GC) and germline testing (GT) referral and acceptance rates.

Methods. We performed a retrospective cohort study of women who underwent a hysterectomy for endometrial cancer at Barnes Jewish Hospital in St. Louis, MO between 1/1/2011 and 12/31/2013 ($n = 637$). An immunohistochemistry-based (IHC) universal screening protocol for Lynch syndrome was initiated on 12/17/2012. The cohorts consisted of women presenting prior to (Pre-Em-USP; $n = 395$) and those presenting following (Em-USP; $n = 242$) initiation of the universal screening protocol. GC and GT referrals were based on risk factors and/or IHC results. Comparisons were made using the Fisher's exact test and the Kruskal–Wallis test.

Results. A greater proportion of individuals in the Em-USP cohort underwent GT than in Pre-Em-USP (9.1% vs 4.8%, $p < 0.05$). Of individuals with an IHC screening result suggestive of LS, those within the Em-USP cohort were significantly more likely to accept GC compared to those in the Pre-Em-USP cohort (95% vs 64%, $p = 0.02$). Specifically within the Em-USP cohort, patients referred to GC due to a concerning IHC screening result, versus those who were referred based on other risk factors, had a higher counseling acceptance rate (95% vs 61%, $p = 0.03$) and underwent genetic testing more readily (76% vs 30%, $p < 0.001$).

Conclusions. Implementation of an IHC-based universal screening protocol for LS in endometrial cancer leads to higher acceptance of genetic counseling and higher rates of genetic testing compared to referral based on risk factors alone.

Introduction

Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant cancer syndrome, caused by inactivating germline mutations in one or more mismatch repair (MMR) genes [1]. These genes behave as tumor suppressors and the most clinically relevant include *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Women with LS are at an increased risk of developing colorectal, endometrial, ovarian, gastric, urinary tract and other cancers [2,3]. A mismatch repair defect in one of the four most commonly mutated genes confers a significantly increased lifetime risk of developing endometrial cancer and 2–5% of all patients with endometrial cancer are mutation carriers [4,5]. Since almost half of the women with LS will present with endometrial cancer as their first malignancy [6], it is essential to identify these individuals in order to refer these women and their family members for proper cancer screening and prevention.

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Screening for LS was traditionally based on family history using Amsterdam Criteria, initially developed primarily for individuals presenting with colorectal cancer [7–9]. These methods have been found to have low sensitivity, particularly in endometrial cancer patients, and may miss a significant number of patients with a mismatch repair defect [4,10]. Patient derived histories are also fraught with errors arising from patients' lack of knowledge or recall of family history and providers' difficulty with eliciting a good family history [11,12]. Molecular screening of the tumors for the presence of MMR proteins in the nuclei using immunohistochemistry (IHC) is an alternative method of screening with sensitivity ranging between 86 and 100% [13]. IHC has been implemented as part of the universal screening protocols in colorectal cancers after a recommendation from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group that it should be performed on all newly diagnosed colon cancer patients [14]. While there is no consensus regarding what the optimal methods of LS screening should be used for endometrial cancer patients, the Society of Gynecologic Oncology recommended selectively screening for all new endometrial cancer patients younger than 60 years old for LS using IHC [15]. However, there is a growing interest in implementation of IHC as part of the screening protocols for LS in endometrial cancer patients [16–19].

Screening success should reflect not only detection rates of LS, but also whether the information is appropriately utilized in order to yield clinical relevance. One of the goals of obtaining a sensitive screening strategy is to be able to provide the appropriate counseling regarding genetic testing and subsequent cancer screening and prevention to patients and their families. This is best accomplished when access to a genetic counselor is easily available and when these counselors are involved in the referral process [20].

Our institution implemented a universal screening protocol (Em-USP) for all endometrial cancer patients undergoing hysterectomy (Fig. 1). Prior to the Em-USP, IHC for MMR enzymes and/or genetic counseling referrals were initiated by the gynecologic oncology surgeon and genetic counselor after review of endometrial pathology and reported family or personal history of cancer. Here we report our experience with LS detection and genetic counseling referral prior to and following the Em-USP in order to compare the two different screening methods. Our primary objective was to determine whether rates of genetic counseling and genetic testing were affected by initiation of Em-USP.

Methods

We conducted a retrospective cohort study of all women who underwent a hysterectomy for endometrial cancer at Barnes Jewish Hospital in St. Louis Missouri between January 1, 2011 and December 31, 2013. Prior to initiation of the study, Institutional Review Board approval was obtained from the Human Research Protection Office at Washington University in St. Louis.

Women included in the study had a new diagnosis of endometrial carcinoma. All histologies of endometrial carcinomas, endometrioid and non-endometrioid, were included. Patients with uterine sarcomas were excluded.

Prior to the implementation of Em-USP, cases were referred to IHC for MMR enzymes based on age of diagnosis, tumor histology, personal

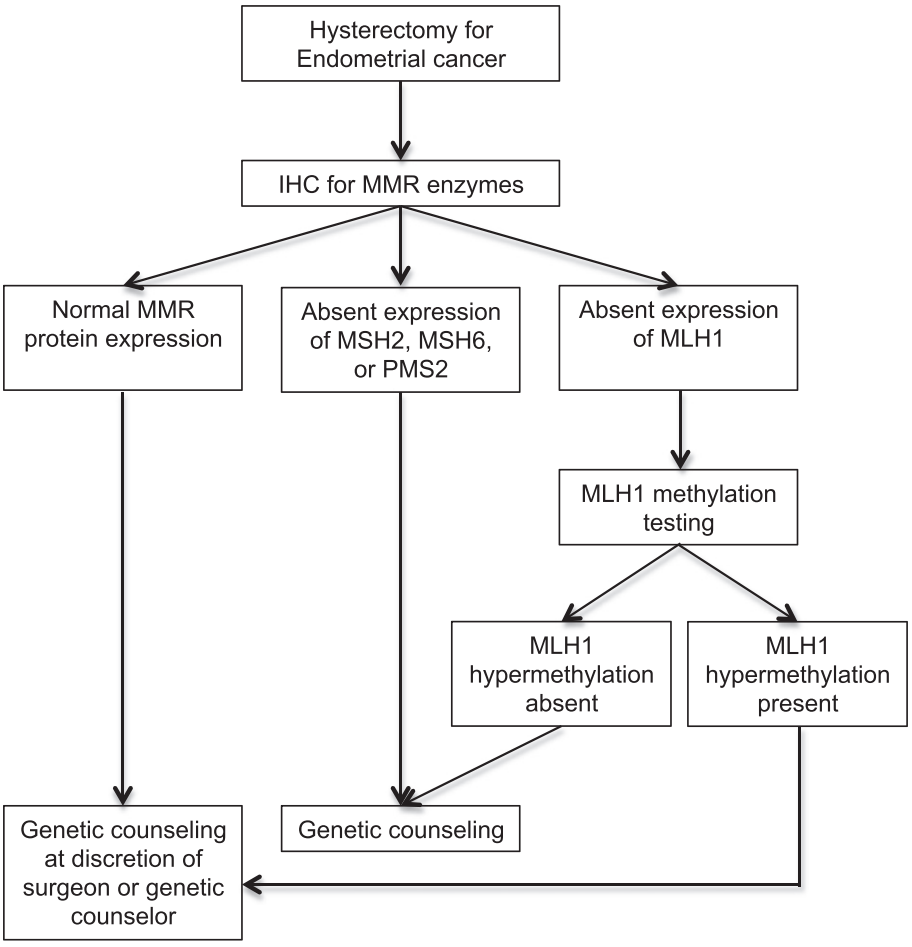

Fig. 1. Endometrial cancer universal screening protocol. IHC, immunohistochemistry; MMR, mismatch repair.