

Lynch Syndrome Related Endometrial Cancer: Aspects and Concerns

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Lynch Syndrome (LS), or Hereditary Non-Polyposis Colon Cancer (HNPCC), is caused by a germline mutation in one of several DNA Mismatch Repair (MMR) genes. Recently, researchers pay closer attention to LS-related Endometrial Cancer (EC), which typically presents as a sentinel cancer up to 40-60% of the cases [1]. Such unique clinical manifestation of LS-related EC will certainly have the potential to influence early detection, screening, and prevention of LS-related non-endometrial cancers, which classically have more aggressive biological behavior and subsequently worse prognosis compared to that of LS-EC. Therefore, many countries, including United States, have started screening patients with EC to identify those with LS, thereby leading to earlier screening for Colorectal Cancers (CRC). Earlier screening would aim to either prevent CRC or detect it in earlier stages [2]. It may be a cost-effective approach since the mortality of CRC is higher than that of EC [2]. Although such understanding has been nationally recognized these years in the literature in the field of gynecology and pathology, many physicians, mainly gynecologists and pathologists, and health care providers are not aware of the clinicopathologic features of LS-related EC. They do not know when a LS-related EC should be considered and how to screen such patients for a possible LS. In this editorial commentary, we provide some guidelines to identify patients with LS from those EC presenters from both clinical and pathologic perspectives and propose an effective screening method for LS in individuals with endometrial cancer.

The clinical clues suggestive of LS-related EC: As studied extensively in recent years, researchers have gradually found that patients with LS-related EC have some features, which are different from EC patients in general. Patients with LS-related EC are often younger than average age of non LS-related EC patients [3]. Particularly, such patients show no evidence of estrogen overstimulation such as obesity, diabetes, exogenous estrogen usage, or polycystic ovarian syndrome [4]. The unopposed estrogen stimulation, either endogenous or exogenous, is characteristic of non LS-related EC in young women [4]. The LS-related EC patients may present irregular vaginal bleeding, but it is less likely to be found to have endometrial hyperplasia prior to EC diagnosis [4]. Additionally, patients with LS-related EC have a tendency to have a synchronous or metachronous ovarian cancer, particularly ovarian clear cell carcinoma [1, 5]. Clinicians should think of a possible LS-related EC when the above patients are encountered in the clinic.

The pathologic findings suggestive of LS-related EC: After studying LS-related EC in detail, researchers found such cancers have, some pathologic characteristics are more frequent than those found in non LS-related ECs. First, LS-related ECs have a tendency to involve low uterine segment (LUS) [6], which may be more associated with *hMSH2* mutation [7]. Second, LS-related ECs tend to be more histologically diverse and can include dominant endometrioid type and occasional non-endometrioid histotypes [8-10]. Third, other microscopic features found in LS-related ECs include poor differentiation, mucinous features, signet ring cell differentiation, mixed tumor histology, tumor cells growing in a medullary-type pattern, increased tumor-infiltrating lymphocytes, and a Crohn-like inflammatory infiltrate at the tumor

invading front or periphery [11]. Pathologists should be aware of a possible linkage to LS-related EC when they encounter these unusual pathologic features.

Laboratory screening test for Lynch syndrome: The main function of MMR genes and corresponding proteins is to maintain genomic stability by correcting mismatches generated during DNA replication. The most important MMR genes included MLH1, PMS2, MSH2 and MSH6. Mutations or malfunction of such MMR genes will result in a mutated phenotype and DNA microsatellite instability, which promotes cancer formation [12]. The loss of these MMR proteins in cancer tissue is currently to be easily detected by routine Immuno histochemistry (IHC) [4]. This simple method makes LS screening from those EC patients possible. Practically, each of these protein IHC test can be performed using formalin-fixed, paraffin-embedded tissues and commercially available antibodies. Although methods wise it is easily carried out, we are aware of that the tests require special molecular pathology training for those pathologists who interpret the test. Such screening tests can be done either in CAP accredited pathology laboratories or in commercial labs. Positive finding of a particular MMR protein loss in cancer tissue is only suggestive of possible LS. Definitive germline testing for MMR gene mutations is determined by a genetics counselor and carried out by DNA sequencing analysis of white blood cells from peripheral blood.

Which patients with EC should be evaluated for LS? Nationally, universal screening for LS in patients with EC has been implemented in several cancer centers [13,14]. However, the incidence in unselected populations of LS in EC patients is approximately 2.3% [11], which may not cost-effective for universal screening. We therefore recommend that all EC patients with above mentioned clinicopathologic characteristics being screened for LS by using IHC method. Only those positive candidates showing loss of one or more MMR protein expression in cancer tissue after evaluation by a qualified pathologist or molecular pathologist can be considered for germline testing by a genetics counselor.

In conclusion, EC is the most common gynecologic malignancy and is the sentinel event in LS 50% of the time. Although the above clinicopathologic findings are neither specific nor sensitive, both gynecologists and pathologists are in a position to identify EC patients who may be presenting with a sentinel manifestation of LS. Close interaction between gynecologists and gynecologic pathologists will

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Received June 15, 2013; Accepted June 17, 2013; Published June 19, 2013

Citation: Wang Y, Wang Y, Zheng W (2013) Lynch Syndrome Related Endometrial Cancer: Aspects and Concerns. J Clin Exp Pathol 3: e117. doi:10.4172/2161-0681.1000e117

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further facilitate identifying LS in clinical practice. Clinicopathologic characteristics may provide important clues for identifying LS-related EC. Then the screening test will be offered selectively rather than universally. We believe that such screening will provide more benefits for patients with LS.

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