Lynch Syndrome
Female Genital Tract Cancer Diagnosis and Screening

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KEYWORDS

• Lynch syndrome • Hereditary nonpolyposis cancer syndrome • Mismatch repair proteins
• Microsatellite instability • Endometrial cancer • Ovarian cancer

ABSTRACT

Lynch syndrome is responsible for approximately 5% of endometrial cancers and 1% of ovarian cancers. The molecular basis for Lynch syndrome is a heritable functional deficiency in the DNA mismatch repair system, typically due to a germline mutation. This review discusses the rationales and relative merits of current Lynch syndrome screening tests for endometrial and ovarian cancers and provides pathologists with an informed algorithmic approach to Lynch syndrome testing in gynecologic cancers. Pitfalls in test interpretation and strategies to resolve discordant test results are presented. The potential role for next-generation sequencing panels in future screening efforts is discussed.

OVERVIEW

Lynch syndrome (LS), also known as Hereditary Nonpolyposis Colorectal Carcinoma (HNPCC) is an autosomal dominant cancer syndrome caused by inactivating germline mutations in the DNA mismatch repair (MMR) genes. The most frequent clinically relevant mutations occur in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes. Patients with LS are at increased risk for multiple malignancies, including cancers of the colorectum, endometrium, ovary, stomach, urinary tract, hepatobiliary tract, small intestine, sebaceous gland, and brain.[1–3] Because LS has traditionally been approached as a colorectal carcinoma–dominated syndrome, screening strategies have centered on colon cancer. However, women with LS are at equal, if not higher, risk for development of gynecologic malignancies when compared with their risk for colon cancer.[1] Moreover, more than half of affected patients present with a gynecologic malignancy, usually endometrial cancer, as their sentinel cancer.[4] The frequency of LS germline mutations in endometrial carcinomas has been estimated at 1.8% to 2.1%, which is similar to that in colon cancer.[5,6] However, recent literature indicates this may be closer to 5.9% in unselected patients with endometrial cancer.[5,7,8] Moreover, the lifetime risk for development of endometrial carcinoma in these patients (up to 60%) may exceed that for colorectal carcinoma.[1,2] For comparison, the current estimated lifetime risk for developing endometrial cancer in the general population is 2% to 3% for the average woman. LS accounts for approximately 2% of all ovarian cancers.[9] The reported lifetime risk of ovarian cancer in LS is 4% to 12%[1,3,9–16] Risk for ovarian cancer appears to be particularly high for patients with *MSH2* and *MSH6* mutations.[14,15] Patients with LS often present with ovarian tumors at relatively younger age (mean 40–48 years); unlike endometrial carcinoma in LS, most patients with ovarian cancer are younger than 50 years of age.[15,16]

Because a substantial number of women with LS first present with a gynecologic cancer, gynecologists and pathologists have the opportunity to identify women at potential risk for synchronous and metachronous tumors, particularly colon

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cancer.[1,17] The time to development of a second cancer varies with a median time of 11 years for patients with endometrial cancer and 5.5 years for patients first diagnosed with ovarian cancer; timely detection of LS in these patients and their family members could lead to appropriate surveillance measures, and decreased morbidity and mortality from metachronous colon cancer.[4]

FUNCTION OF DNA MISMATCH REPAIR GENES

Mutations in the DNA-MMR genes involved in LS are typically associated with loss of function and high microsatellite instability (MSI-H).[18] Microsatellites are repetitive widely dispersed DNA sequences consisting of mono-, di-, or higher-order nucleotide repeats that are prone to replication errors due to inefficient binding of DNA polymerases. Normally these errors are corrected by the DNA-MMR system (DNA-MMR). Deficiencies in the DNA-MMR therefore results in MSI-H.[19] Microsatellite instability occurs as a result of genetic (MMR gene mutation) or epigenetic (most commonly, *MLH1* promoter methylation) alterations.[20] Of the 20% to 25% of endometrial carcinomas that are MSI-H, 75% result from sporadic *MLH1* promoter methylation. The minority are LS-associated tumors. Therefore, LS and MSI should not be used synonymously.

LYNCH SYNDROME FEMALE GENITAL TRACT TUMORS

LS endometrial cancers do not exhibit site-specific or morphology-specific features to the degree that is seen in LS colorectal cancer. Although it has been suggested that as many as one-third of tumors arising in the lower uterine segment may be LS, in reality it is probably more on the order of 10% to 15%.[21,22] The endometrial carcinomas can show a wide spectrum of histologic subtypes. Endometrioid carcinomas are the most common type, but nonendometrioid carcinomas, including serous carcinoma, clear cell carcinoma, and carcinosarcoma, are also observed in LS, often at comparatively younger ages than is typically associated with these tumors.[21,23,24] Several histologic features of uterine endometrioid cancers (eg, tumor-infiltrating lymphocytes, prominent peritumoral lymphocytes, tumor heterogeneity, undifferentiated or dedifferentiated histology) have been linked to microsatellite instability, but their predictive value in identifying a potential germline MMR protein mutation is less certain.[8,25–29]

One of the endometrial cancer subtypes that has been associated with microsatellite instability is undifferentiated endometrioid carcinoma (**Fig. 1**). Undifferentiated endometrial carcinoma is composed of solid, discohesive sheets of round or polygonal cells with vesicular nuclei and prominent nucleoli; no gland formation is present (see **Fig. 1**).[30] A myxoid matrix, rhabdoid cells, or lymphoepitheliomalike areas, defined as sheets of undifferentiated cells with a prominent lymphocytic infiltrate may be seen in undifferentiated endometrial carcinoma. When undifferentiated carcinoma is accompanied by a distinct component of well to moderately differentiated endometrioid carcinoma, it has been designated as dedifferentiated endometrial carcinoma.[31] Undifferentiated/dedifferentiated endometrial carcinomas are associated with MMR abnormalities and MSI-H.[32] Most are sporadic and associated with *MLH1* promoter methylation.[23,25] Undifferentiated and dedifferentiated carcinomas appear to be particularly associated with abnormalities of *MLH1*/*PMS2*, both in the form of promoter methylation and germline mutations (see **Fig. 1**).[21]

Key Features
MORPHOLOGY OF MICROSATELLITE UNSTABLE ENDOMETRIOID ADENOCARCINOMA

- Prominent peritumoral lymphocytes (apparent at scanning magnification)
- Increased tumor-infiltrating lymphocytes (TILs); that is, lymphocytes located within the boundary of tumor cell nests or glands (TILs >42 per 10 high-power fields)
- Tumor heterogeneity defined as 2 morphologically distinct tumor populations juxtaposed but not intimately admixed, each constituting at least 10% of the tumor volume
- Undifferentiated or dedifferentiated histology

In contrast, the spectrum of ovarian tumors seen in LS differs from that of the general population. Most LS ovarian cancers are nonserous; most are endometrioid, clear cell, or undifferentiated carcinomas.[14,15] The endometrioid carcinomas are usually well to moderately differentiated, present at early stages, and appear to pursue a favorable clinical course.[12,15] Ovarian clear cell carcinoma, particularly in younger patients, is also strongly associated with LS; up to 14% to 17% of ovarian clear cell carcinomas are associated with MMR defects.[14,15] Approximately 10% of all ovarian carcinomas in patients 50 years of age or younger are associated with MMR defects, and most (60%) of these are clear cell carcinomas, with the remainder showing undifferentiated or endometrioid histology.[14]