Case 7: Lynch syndrome

Rachel is a 44-year-old woman with a body mass index (BMI) of 32. She presented with abnormal uterine bleeding to her gynecologist, who performed an endometrial biopsy that indicated endometrial adenocarcinoma of endometrioid histology. She was referred to a gynecologic oncologist and underwent a total hysterectomy and bilateral salpingo-oophorectomy. The pathology from this procedure confirmed that she has stage I disease. She required no adjuvant chemotherapy or radiation therapy.

Rachel’s family history is significant for colon cancer. Her mother was diagnosed with colon cancer at age 66. Her paternal aunt was diagnosed with endometrial cancer at age 67. Rachel wonders if her endometrial cancer has a hereditary component.

Fig. 1. Pedigree of a family with Lynch syndrome. Members of the family have colorectal and endometrial cancer.

Legend

Female
Male
Affected with trait
Deceased
Twins
Adopted
Miscarriage
Marriage line
Generation number
Line of descent
Sibling line
What is Lynch syndrome?

Lynch syndrome is the most common form of an inherited predisposition for colon and endometrial cancer and is inherited in an autosomal dominant pattern, meaning that a parent of either sex with a mutation has a 50% chance of passing it on to a child of either sex. Lynch syndrome is also associated with an increased chance of developing cancers in other organs such as the stomach, ovary, and ureter/renal pelvis over a lifetime. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair. According to NCCN guidelines, surveillance for colon cancer should begin at 20-25 years of age (or 2-5 years prior to the earliest colon cancer in the family if it was diagnosed before age 25) and is repeated on a 1- to 2-year basis depending on the findings of the previous colonoscopy. Colon polyps associated with Lynch syndrome can progress to a malignancy in a 1- to 2-year period, compared to the often-quoted 10-year period for a sporadic colon polyp.

The chances of developing cancer and the ages at which they might develop can vary depending on which DNA mismatch repair gene is affected. Cancer rates are much higher in MLH1 and/or MSH2 mutation carriers compared to MSH6 and/or PMS2 mutation carriers. The lifetime chance of developing endometrial cancer with an MLH1 or MSH2 mutation is estimated to range from 25 to 60% (mean age of onset 48 to 62 years) versus a 15% lifetime chance in PMS2 mutation carriers (mean age of onset at 49 years). In addition, the chance of developing ovarian cancer for MLH1 and MSH2 mutation carriers by age 70 is estimated to be 11 to 24% (mean age of onset of 43 to 45 years) versus a much lower risk for MSH6 and PMS2 mutation carriers based on limited data. Endometrioid ovarian cancer is the most common histologic type seen in Lynch syndrome. Because of the variable risk of cancer associated with each specific Lynch mutation, it is important to individualize recommendations based on age and mutation.

A gynecologic malignancy may be the first presentation for a woman with Lynch syndrome; however, she is at risk for other malignancies, including a 40 to 60% lifetime risk of colon cancer. The gynecologic oncologist is an important provider to recognize the association and initiate surveillance to prevent a second primary tumor and further cancers in the family.

Who should be tested for Lynch syndrome?

Traditionally, testing for Lynch syndrome was recommended based on meeting relatively strict rules for personal and/or family history of colorectal and Lynch-related cancers (Bethesda or Amsterdam guidelines). However, these guidelines miss a large number of families that carry Lynch syndrome mutations. Since approximately 3 to 5% of all colorectal cancers are associated with Lynch syndrome, NCCN guidelines now recommend that all patients with colorectal and endometrial cancer be screened for Lynch syndrome. A Centers for Disease Control and Prevention working group has endorsed that policy as cost-effective.

When universal screening is not in place, SGO recommends that all patients with endometrial cancer undergo assessment of their personal and family history, with testing recommended for those with other Lynch syndrome-related tumors present.

How is testing done for Lynch syndrome?

Like women with personal or family histories suggestive of HBOC syndrome, those with personal and family histories suggestive of Lynch syndrome can be referred for genetic risk evaluation and undergo germline genetic testing. However, women who are diagnosed with a Lynch syndrome-related cancers such as endometrial or colorectal cancer, can have tumor screening as a first step. The tumor can be assessed with immunohistochemistry (IHC) for the presence or absence of DNA mismatch repair proteins, including MLH1, MSH2, MSH6, and PMS2. When expression of one or more of these proteins is absent, suspicion for Lynch syndrome increases. However, promoter methylation of MLH1 must be considered when its expression is abnormal, as it is a common event in sporadic endometrial cancer. The tumor can also be assessed for microsatellite instability (MSI), which is usually quantified as high or low. Over 90% of Lynch syndrome tumors lack expression of one of the IHC proteins and/or are MSI-high. Algorithms vary between institutions as to whether IHC alone, MSI alone, or IHC and MSI in combination are used for Lynch syndrome screening. In patients such as Rachel who already meet Amsterdam criteria for Lynch syndrome based on personal and family history of cancer, they can be referred for germline genetic testing directly without first undergoing tumor testing. One consideration in this circumstance is that if germline testing were negative for a mutation, knowledge of tumor MSI and/or IHC status might make the patient eligible for immunotherapy if the tumor is documented to have mismatch repair deficiency.

When abnormal tumor test results are present, referral to a genetics professional is recommended for germline testing to confirm the presence of a Lynch syndrome mutation.
Patients who are unaffected by cancer may undergo germline testing based on the suspected or known presence of a mutation in family members. In addition, Lynch syndrome genes are included in many multi-gene panels assessing hereditary cancer risk.

What surveillance is recommended for women with Lynch syndrome?

ACOG, NCCN, and SGO have the following recommendations for women with Lynch syndrome:

- Colonoscopy every 1 to 2 years, beginning at age 20 to 25 years, or 2 to 5 years before the earliest cancer diagnosis in the family, whichever is earlier.
- Keep menstrual calendar and report abnormal bleeding for prompt evaluation
- Endometrial biopsy every 1 to 2 years can be considered starting at age 30-35.
- Transvaginal ultrasound can be considered after menopause.
- Hysterectomy with bilateral salpingo-oophorectomy can be considered based on desire for childbearing, comorbidities, family history, and specific LS gene involved.

Consideration also may be given to risk-reducing strategies such as the use of hormonal contraception, which has been shown to decrease endometrial, ovarian, and colon cancer risk substantially, especially with 5 years or more of use.

References


