Diagnosis and Management of Lynch Syndrome

Luv Hajirawala, M.D., M.S.[1] • Jeffrey S. Barton, M.D.[2]

1 Department of Surgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana
2 Section of Colorectal Surgery, Department of Surgery, Louisiana State University Health Sciences Center, New Orleans, Louisiana

CASE SUMMARY: A 56-year-old man with a history of hypertension and hyperlipidemia was referred by gastroenterology for bleeding per rectum. Because of a family history of colon cancer, he had several prior colonoscopies, most recently 3 years ago, without evidence of pathology. His mother was diagnosed with colon cancer in her mid-40s. His current colonoscopy demonstrated a 2.4×1.5 cm cecal adenocarcinoma. Staging workup revealed no evidence of metastatic disease. Because of the patient's family history, the specimen was further evaluated and found to have high microsatellite instability (MSI-H). The patient was referred to a genetic counselor and found to have a germline pathogenic variant in MSH6 on gene panel testing. The patient did not have a family history of any extracolonic malignancies.

The patient underwent an uncomplicated laparoscopic total abdominal colectomy with ileorectal anastomosis, which revealed a T2N0Mx adenocarcinoma with abundant peritumoral lymphocytes. He was discharged on postoperative day 2, and recuperated appropriately from surgery. Follow-up surveillance proctoscopy showed no evidence of disease. His sole offspring, a 25-year-old man, was negative for a pathogenic variant in *MSH6* and had no polyps on colonoscopy. His siblings did demonstrate a pathogenic variant in *MSH6* and are currently opting for annual surveillance colonoscopy.

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Correspondence: Luv Hajirawala, M.D., M.S., LSU New Orleans Department of Surgery, 1542 Tulane Ave, 7th Flr, New Orleans, LA 70112. E-mail: lhajir@lsuhsc.edu

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CLINICAL QUESTIONS

- Who should undergo genetic testing for Lynch syndrome?
- What extracolonic malignancies should the surgeon consider during surgical planning for patients with Lynch syndrome?
- What risk-reducing operations should be offered to patients with Lynch syndrome?

BACKGROUND

Familial colorectal cancer (CRC) accounts for 20% to 30% of all cases, with an estimated 3% to 5% having an identifiable Mendelian etiology.[1] Lynch syndrome (LS) is the most prevalent of these CRC syndromes. Lynch syndrome is caused by autosomal dominant germline pathogenic variants in DNA mismatch repair genes (MMR), including *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[2] Germline pathogenic variants in *EPCAM* cause hereditary silencing of *MSH2*, producing an identical phenotype.[2] Identification of the causative pathogenic variant can be used to evaluate family members and guide surveillance.

PRESENTATION AND DIAGNOSIS

Lynch syndrome-associated CRC tends to present earlier than sporadic CRC, in the fifth or sixth decade of life.[3] Pathogenic variants in *MLH1* and *MSH2* confer a 30% to 74% lifetime risk of developing CRC, whereas *PMS2* (15%–20%) and *MSH6* (10%–22%) have slightly lower rates.[3] Malignant degeneration of adenomas can occur over 2 to 3 years in LS compared to 4 to 10 years in the general population, with higher rates of high-grade dysplasia in polyps in patients with LS.[4,5] Adenomas in LS tend to be nonpolypoid, large, and flat.[6] Cancers in patients with LS demonstrate a predilection toward the right colon, although synchronous or metachronous left-sided lesions are frequently reported.[3]

Histologically, CRC in LS tends to be poorly differentiated, to be abundant in extracellular mucin, and can demonstrate signet cell features.[7] Tumors tend to show a

TABLE 1. Bethesda and Amsterdam criteria

Amsterdam II Criteria[a] (Sensitivity 22%; specificity 98%)
All criteria must be met
Three or more relatives with histologically confirmed colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis; one affected relative being a first-degree relative of the other 2; FAP should be excluded.
Two or more successive generations are affected.
At least 1 relative diagnosed before the age of 50.
Revised Bethesda Guidelines[b] (Sensitivity 82%; specificity 77%)
One or more of the following criteria must be met
Colorectal cancer before the age of 50 years
Synchronous or metachronous colorectal cancer of other HNPCC-related tumors (regardless of age)
Colorectal cancer with MSI-high morphology before the age of 60 years
Colorectal cancer (regardless of age) and a first-degree relative with colorectal cancer or an HNPCC-related tumor before the age of 50 years
Colorectal cancer (regardless of age) and 2 or more first- or second-degree relatives diagnosed with colorectal cancer or an HNPCC-related tumor (regardless of age)

FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; MSI = microsatellite instability.
[a]Source: Vasen et al.[9]
[b]Source: Umar et al.[10]

lymphoid host response, with a Crohn's-like pattern and/or peritumoral lymphocytes.[7] Stage-for-stage, patients with LS have improved survival from CRC compared with patients with sporadic CRC.[3]

Patients with LS have a propensity to develop extracolonic malignancies. The highest risk is for endometrial cancer, which is most prominent in patients with *MSH6* mutation.[3] Patients with LS also have a higher risk of urothelial carcinoma, in particular, in pathogenic variants of *MSH2*. Lynch syndrome may also confer increased risk of adenocarcinoma of the ovary, stomach, hepatobiliary tract, and small bowel; glioblastoma; and cutaneous sebaceous neoplasms (Muir Torre).[3] Phenotypic stigmata of LS such as café-au-lait spots, cutaneous sebaceous gland tumors, and keratoacanthomas may be observed, in particular, in patients homozygous for LS-causing mutations.[3]

A detailed family history is paramount in evaluation of LS, and should be obtained across 3 generations to help guide decisions for testing.[8] Although the Bethesda and Amsterdam Criteria (Table 1) are helpful in identifying patients at risk for LS, the identification of causative genes for LS has led to more direct means of screening and diagnosis (see Evaluation and Treatment Algorithm). The National Comprehensive Cancer Network and Multi Society Task Force endorse universal screening of all CRC using immunohistochemistry (IHC) or MSI testing on tumor specimens.[3,8] Immunohistochemistry entails staining tumor tissue for protein expression of 4 MMR genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Abnormal expression of the gene products may indicate an underlying germline pathogenic variant. Lack of *MLH1* expression requires further evaluation because it may be caused by epigenetic silencing through hypermethylation. This can be verified by assessing for abnormal methylation of *MLH1* gene, or by assessing for the V600E mutation in *BRAF* gene, which is present in 60% of sporadic cancers but virtually absent in LS.[2] The presence of either of these findings is consistent with spontaneous CRC, and should be treated as such. In the absence of epigenetic anomalies, absent IHC staining of one or more MMR gene products should prompt germline genetic testing (see Evaluation and Treatment Algorithm). Primary CRC or endometrial tissue is preferred for IHC, but larger adenomas, sebaceous neoplasms, or CRC metastases can also be used for screening for LS when primary tumor tissue is unavailable.[8] Caution should be used in the interpretation of IHC on postradiation rectal cancer tissue because of a higher risk of false abnormal result; pretreatment tissue is preferred when available.[8]

Microsatellite instability is the hallmark of LS-related malignancies. DNA microsatellites are tandem sequences of nucleotide repeats that are susceptible to replication errors, in particular, when MMR function is impaired. This results in abnormally increased or decreased numbers of microsatellites, denoted microsatellite instability high (MSI-H) or microsatellite instability low (MSI-L).[2] Polymerase chain reaction is used to measure the number of microsatellites in DNA from tumor cells to assess for MSI.[2] Because virtually all LS tumors exhibit MSI, further germline testing is usually unnecessary for microsatellite stable tumors. MSI-H is associated with LS and should prompt further testing.

Germline testing for MMR gene mutations is used to diagnose LS.[3,8] Before testing, patients should undergo genetic counseling to discuss the benefits and implications of identifying a germline mutation, both for the patient and the family.[3]

MANAGEMENT

Treatment for patients who develop cancer or premalignant polyps unamenable to endoscopic removal is colectomy with appropriate lymphadenectomy. Segmental colon resection for CRC in patients with LS has been associated with a higher cumulative risk of development of metachronous CRC than subtotal colectomy (HR 0.2, $p = 0.001$), although no survival benefit has been observed with extended resection.[3,10] The National Comprehensive Cancer Network and Multi Society Task Force recommend total abdominal colectomy with ileorectal anastomosis for individuals with known LS who develop CRC.[3,8] The benefit of risk reduction by a total abdominal colectomy should be evaluated against risks of bowel dysfunction and quality of life, especially in elderly patients.[3] This is of greater importance in patients with LS who develop rectal cancer, because total proctocolectomy with an end ileos-

tomy or ileal reservoir would confer a much greater functional impact on patients than a mere resection.[11]

The management of patients with LS requires multiorgan consideration because of the colonic and extracolonic manifestations of the disease. Although specific mutations are associated with higher risk of certain malignancies, a general knowledge of the risks of extracolonic disease can help guide the colorectal surgeon's operative evaluation and long-term screening. Given this, consideration should be given to additional workup of patients with LS before operative intervention. Evaluation for concurrent endometrial carcinoma is advised by the authors before colorectal resection, in particular, for women carrying a pathogenic variant in *MSH6*. Urinalysis may be performed to evaluate for the possible presence of urothelial carcinoma, especially in the patients with a pathogenic variant in MSH2. In the event of synchronous extracolonic malignancy, consideration should be given to simultaneous or staged operative interventions.

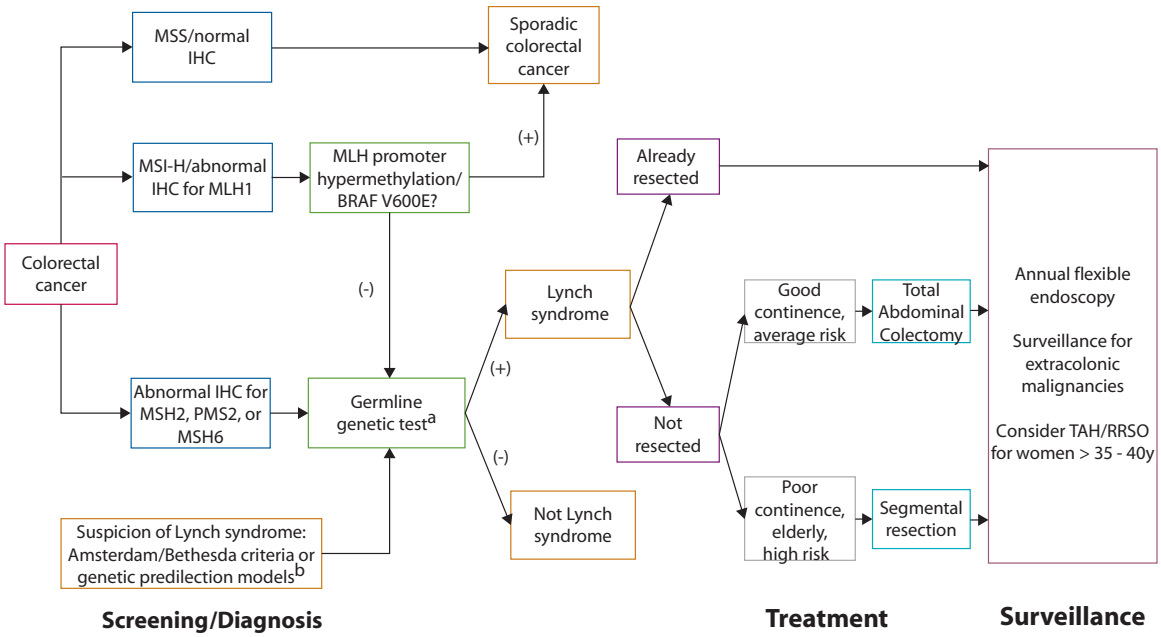
Many patients will be diagnosed with LS following resection of CRC. Concurrent or staged risk reduction procedures for reproductive organ malignancies should be considered for women with LS. Hysterectomy and risk-reducing salpingo-oophorectomy provide excellent prophylaxis against endometrial and ovarian cancers.[3] Timing of hysterectomy and risk-reducing salpingo-oophorectomy should be individualized based on patient preference, childbearing status, family history, and specific mutations.[8] Close surveillance of residual nonneoplastic colorectum is crucial. Patients with LS who underwent segmental colectomy should get an annual surveillance colonoscopy.[8,10] Although there is paucity of data evaluating the benefit of yearly endoscopic surveillance for patients with LS after subtotal colectomy, these patients should be followed closely because of the high risk of metachronous malignancy.[10]

Finally, chemoprevention with aspirin has shown promise for reducing the risk of colon cancer in LS, and studies evaluating optimal dosage are currently underway. In the absence of conclusive data, chemoprevention with aspirin should be considered individually based on patient-specific risks and benefits.[3]

CONCLUSION

Because our understanding of LS has evolved with the discovery of causative mutations, so should our management of patients with LS. The choice of operation and concurrent surgical planning are significantly changed by the preoperative diagnosis of LS, and so consideration should be given to preoperative testing for high-risk individuals. Patients diagnosed postoperatively should be counseled on risk-reducing surgeries and surveillance of both colorectal and extracolonic disease. A strong understanding of, and index of suspicion for, LS can benefit both the colorectal surgeon and the patient with CRC.

EVALUATION AND TREATMENT ALGORITHM



NOTE. Diagnosis and treatment algorithm for patients with Lynch syndrome. [a]Germline genetic testing refers to multiple tests available to detect germline mutations for Lynch syndrome. Some tests are specific for 1 mutation and can be used to rule out a known familial mutation in the patient, either based on protein deficiency on the IHC/MMR tests or family history of a known mutation. Genetic panels that detect multiple mutations can be used when a causative mutation is not known. [b]Clinical prediction algorithms, such as PREMM and MMRPRO, estimate the probability of an individual carrying germline mutation resulting in LS. Probability >5% should be followed by genetic counseling and/or germline testing. IHC = immunohistochemistry; LS = Lynch syndrome; MMR = measles, mumps, and rubella; MSI = microsatellite instability; MSS = microsatellite stable; RRSO = risk-reducing salpingo-oophorectomy; TAH = total abdominal hysterectomy.

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Expert Commentary on the Diagnosis and Management of Lynch Syndrome

Matthew F. Kalady, M.D.

Department of Colorectal Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio

I am fortunate to work in a hospital that manages a large hereditary colorectal cancer (CRC) syndrome population within our registry. We have a fantastic multidisciplinary team composed of colleagues in various specialties who have expertise and knowledge of how to diagnose, evaluate, and treat patients and families with Lynch syndrome (LS). Dealing with hereditary syndrome patients can sometimes be daunting, because the knowledge of the underlying science, associated technology, and, accordingly, the clinical management are frequently changing. However, understanding the basics and how to get more information if needed are important. Caring for patients with LS is also one of the most satisfying parts of my job, because there is continuity of care, an ability to prevent cancers, and an opportunity to impact the entire family.

I congratulate Dr Hajirawala for providing an overview of LS in the case presentation. There are a few points that I want to reiterate and expand on regarding management. First, precise nomenclature is important. As the genetics underlying LS have been elucidated and more is learned about specific cancer predisposition, we are able to develop more personalized approaches. Although family history is the cornerstone, LS is a genetic diagnosis. Patients who have a germline pathogenic variant in 1 of the mismatch repair genes has a diagnosis of LS regardless of their personal or family history. Conversely, patients who meet Amsterdam criteria but do not have a pathogenic variant in a mismatch repair gene do not have LS. People meeting Amsterdam criteria by definition have hereditary nonpolyposis colorectal cancer (HNPCC). To subclassify even further, patients with CRC within HNPCC, but whose tumor is microsatellite stable (mismatch repair proficient), are defined as having familial colorectal cancer type X.[1] Both HNPCC and familial colorectal cancer type X patients have unique risk profiles, and the screening and

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Correspondence: Matthew F. Kalady, M.D., Department of Colorectal Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195. E-mail: kaladym@ccf.org

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management are different from that of LS.[2] In a review of the literature to evaluate the appropriate use of these terms, 33% of articles used the terms incorrectly.[3]

The key to diagnosing LS is to maintain a high suspicion. Risk factors that should raise a red flag include young age of onset; synchronous or metachronous CRC; multiple- or young-onset colorectal adenomas; extracolonic cancers, such as endometrial, ovarian, or gastric; and family history of colonic or extracolonic cancers. Every patient encounter is an opportunity to gather a family cancer history. If LS is suspected, the patient should be counseled and tested. If you are uncomfortable doing that or genetic counseling services are not available at your hospital, then refer the patient to a specialized center or use online genetic counseling services. Many institutions now use some form of universal screening program for LS on resected CRCs, which identifies patients suspected of having LS and requiring additional evaluation. Although a universal screening program helps prevent missing a LS diagnosis on patients with CRC, ideally the diagnosis would be made before the surgery. One additional context in which a patient with LS may be referred is when LS is in the family and a person without any manifestations has a genetic diagnosis. These patients should enter into surveillance programs. Regardless of how patients are identified, the goal is to prevent cancer formation and death from cancer, as well as to provide education and appropriate screening for the patient and his or her family.

Surgical decision-making in LS is based on treating the current cancer, minimizing future CRC risk, and maintaining quality of life and reasonable bowel function.[4] A detailed discussion with each individual patient should be had discussing the risks, benefits, and expectations after a segmental or total colectomy (with rectal preservation and ileorectal anastomosis (IRA)). There have not been any prospective randomized trials that evaluate total abdominal colectomy (TAC) and IRA compared with segmental colectomy with close colonoscopic surveillance. However, there are multiple lines of evidence that support the expert opinion and recommendation for TAC and IRA for colon cancer in LS. Retrospective studies comparing the 2 approaches have consistently shown high rates of metachronous adenomas (including high-risk adenomas) and CRCs. The risk is ≈10% at 10 years and increases over time to as high as 60% at 40 years.[5] Patients may express concern about expected bowel function after an extended resection, but the average bowel movements frequency is ≈4 times daily after an IRA compared with ≈2 times daily after an segmental resection, with minimal impact on overall quality of life. Thus, in my practice, for patients with colon cancer in LS who are medically fit and can tolerate the surgery and the postoperative expectations, they are offered a TAC and IRA. If the patient refuses, if they are not fit for the extended resection, or if the diagnosis is made after a segmental colectomy has already been done, then fastidious annual endoscopic evaluation with polypectomy as encountered is mandatory.

The final point to be made is that LS is a multisystem disease, and knowledge of the other organs at risk is critical to provide appropriate screening and surveillance. Also, because LS is an autosomal dominant hereditary condition, 50% of all first-degree relatives are potentially affected. This needs to be explained in depth to patients with encouragement for them to communicate with their own family members so that they may receive appropriate counseling and testing. Following these basic principles and knowing when and where to ask for assistance will allow for best practice management of these patients and their families.

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