How to Recognize and Manage Hereditary Colon Cancer Syndromes

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Learning Objectives

- To learn features of a patient's personal or family history that suggest a hereditary cancer syndrome.
- To learn the genetic basis for the common known gastrointestinal cancer predisposition syndromes.
- To learn risks and benefits of genetic testing for cancer predisposition.

Clinical Management Points

- Approximately 5% of colorectal cancers are caused by inherited gene mutations associated with Hereditary Nonpolyposis Colorectal Cancer (HNPCC)/Lynch Syndrome, Familial Adenomatous Polyposis (FAP), or the Hamartomatous Polyposis Syndromes.
- Genetic testing is clinically available for several hereditary gastrointestinal cancer syndromes and is part of standard care.
- Patients and family members with a hereditary susceptibility to cancer need intensive surveillance for associated cancers, consideration of prophylactic surgery, and genetic counseling.

Introduction

The majority of cases of gastrointestinal cancer are believed to be sporadic events; however, inherited factors play a role in development of some tumors, with an estimated 5% being attributable to a single gene mutation. Hereditary gastrointestinal cancer syndromes convey a markedly increased risk for developing cancer, and require specific strategies for diagnosis and management.

Lynch Syndrome/ Hereditary Non-polyposis Colorectal Cancer (HNPCC)

Lynch Syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is the most common hereditary colorectal cancer syndrome and is estimated to account for 3-5% of CRC cases. Although the original Lynch syndrome families were identified as having 3 or more cases of CRC with at least one diagnosed at age <50 years as described by the Amsterdam Criteria, additional studies have demonstrated that the cancer spectrum in these families includes other cancers, such as gastrointestinal, gynecologic, urinary tract, and sebaceous neoplasms of the skin. Since as many as 50% of Lynch Syndrome families do not meet the classic Amsterdam criteria, clinical diagnostic criteria have been expanded and modified to improve diagnostic sensitivity. As outlined by the Revised Bethesda Guidelines, Lynch Syndrome should be suspected in families that have multiple relatives affected with CRC and/or related extracolonic tumors and in individuals who are diagnosed with CRC at a young age (age <50), have synchronous or metachronous CRCs or develop multiple HNPCC-associated tumors.

Clinical Features

Colorectal cancer is usually the predominant cancer in most families with Lynch Syndrome. Endometrial (uterine) cancer is the second most common cancer described in Lynch Syndrome families, and women have a 40-60% lifetime risk for developing this malignancy. The lifetime risks for developing other Lynch-associated cancers such as urinary tract cancers, ovarian cancer and other gastrointestinal cancers (stomach, pancreas, small intestine) are also increased for individuals with Lynch Syndrome and are estimated to be between 10-20%. Brain tumors (such as glioblastomas and astrocytomomas) have been described in the Turcot Syndrome variant of Lynch Syndrome. Cutaneous sebaceous adenomas and sebaceous carcinomas are rare skin tumors seen in the Muir-Torre variant.

Genetics

The increased predisposition to developing cancer in Lynch Syndrome is the result of autosomal dominantly-inherited mutations in genes involved in DNA mismatch repair (MMR). Mutations in the genes hMLH1 and hMSH2 account for >80% of the identified MMR alterations in Lynch Syndrome families. Mutations in the MMR gene hMSH6 have been identified in approximately 10% of Lynch Syndrome families, and in hPMS2 in rare families.

The protein products of MMR genes are involved in identifying and repairing errors that arise during DNA replication. In the setting of defective MMR gene function, these errors accumulate in segments of DNA containing repeated sequences known as microsatellites. DNA errors that disrupt the function of genes involved in growth regulation can lead to the development of tumors. More than 90% of the colorectal tumors in Lynch Syndrome patients will demonstrate microsatellite instability (MSI), a characteristic of defective MMR gene function. Analysis of colorectal tumors for expression of MMR proteins MLH1, MSH2, MSH6 and PMS2 reveal loss of staining of the gene with the mutation.
Clinical Management of Lynch Syndrome
The high lifetime risk of colorectal and other extracolonic cancers, the accelerated progression of adenomas to adenocarcinomas, and the young age of onset of colorectal neoplasia require specialized strategies for cancer prevention.

Colorectal Cancer Screening – Individuals who are at risk for Lynch Syndrome should begin having colonoscopies at age 20-25 with repeat examinations every 1-2 years.

Endometrial Cancer Screening – Expert panels recommend that women at risk for Lynch Syndrome undergo endometrial cancer screening with annual transvaginal ultrasound and endometrial biopsy beginning at ages 25-35. At present there are no data to support the efficacy of this endometrial screening regimen and women who have completed childbearing should be counseled to consider prophylactic hysterectomy as a more definitive measure to reduce their cancer risk.

Screening for Other Cancers – Although the risk for other extracolonic cancers is increased in Lynch Syndrome, there is insufficient evidence to definitively recommend screening for many of these other cancers. For urinary tract cancer screening, expert panels have recommended annual urine cytology, although its efficacy remains unproven. Screening for ovarian cancer includes transvaginal ultrasound and checking serum CA-125 levels once yearly. Screening for gastric cancer and small intestinal cancer using upper endoscopy has been proposed by some experts. Individuals with Lynch Syndrome from families with Muir-Torre should have annual dermatologic exams to screen for cutaneous sebaceous neoplasms.

Prophylactic Surgery
Prophylactic surgery may be considered as an alternative to annual screening. For the majority of Lynch syndrome patients who are compliant with surveillance colonoscopies, prophylactic surgery is unlikely to be necessary. For some who develop early or multiple adenomas or for whom colonoscopy is painful, prophylactic colectomy may be a good option. Individuals who develop colorectal neoplasms which require surgical resection should be offered extended resections with a subtotal colectomy, since risk for metachronous lesions is high. Individuals who have had subtotal colectomies can then have screening of their residual colonic mucosa via flexible sigmoidoscopy.

Women should be counseled that there is limited evidence regarding the impact of endometrial screening on morbidity and mortality from endometrial cancer and prophylactic hysterectomy and oophorectomy may be the most effective way to reduce risks of gynecologic cancer.

Clinical Genetic Testing
Genetic testing for MMR gene mutations associated with Lynch Syndrome is increasingly available in clinical settings and provides the opportunity to confirm the diagnosis of Lynch Syndrome in a family and to test other individuals in order to stratify their cancer risk.

The PREMM1,2,6 model is a web-based clinical prediction rule designed to be used by healthcare professionals to estimate the probability that an individual carries a mutation in MLH1 or MSH2, and is available at www.dfci.org/premm. Individuals whose personal and family history produces a PREMM model score of >5% should undergo molecular evaluation for Lynch Syndrome.

The most efficient strategy for genetic testing is to begin genetic evaluation with an individual who has a cancer diagnosis starting with evaluation of a colorectal cancer tumor specimen for features of microsatellite instability (MSI) and loss of immunohistochemical (IHC) staining for MLH1, MSH2, MSH6 and PMS2 proteins. As 90% of the CRC tumors in MMR gene mutation carriers will demonstrate high levels of MSI or abnormal staining for MMR proteins, this pathologic testing can serve as a prescreen to select which individuals should undergo germline testing for MMR mutations.

Two main techniques are therefore used in molecular tumor testing: Immunohistochemistry (IHC) of tumor sections with antibodies specific for MLH1, MSH2, MSH6 and PMS2, which visualizes absence, presence, or reduced level of each protein, and analysis of presence and extent of microsatellite instability (MSI) in DNA extracted from tumors. Both approaches are approximately 90% sensitive, and loss of staining for specific proteins visualized by IHC can predict affected genes reasonably accurately. However, these tests are not diagnostic of Lynch Syndrome, because tumors can also exhibit similar phenotypic characteristics due to acquisition of somatic mutations or epigenetic changes that affect MLH1 expression, and typically, the incidence of these increases with age, reducing the specificity of MSI and IHC testing in older patients. Approximately 15% of sporadic colorectal cancers have MSI. If the tumor shows loss of MLH1 staining, prior screening for a somatic mutation of the BRAF gene can aid in distinguishing sporadic tumors, in which this mutation is common, from Lynch syndrome, in which this is rarely found.

A definitive diagnosis of Lynch syndrome requires genetic testing for germline mutations in the DNA mismatch repair genes involved, and current guidelines recommend this approach for anyone with abnormal MSI or IHC results. Clinical genetic testing for germline mutations in the MLH1, MSH2, MSH6, PMS2 and EPCAM genes can be performed on DNA extracted from a peripheral blood sample. Clinical laboratories
specializing in genetic testing perform full gene sequencing and southern blot analysis for large genomic deletions in these MMR genes. If testing reveals a pathogenic mutation in any of these genes, then testing is considered informative and mutation-specific testing can be offered (at greatly-reduced cost) to other family members to determine who has and has not inherited the genetic predisposition to cancer. If testing in a cancer-affected individual fails to reveal a mutation, then genetic testing is considered uninformative and the clinical determination must be made whether the suspicion for Lynch Syndrome is sufficiently high to recommend Lynch Syndrome cancer surveillance to all members of the family.

**Familial Adenomatous Polyposis (FAP)**

Familial adenomatous polyposis (FAP) is the second most common inherited colorectal cancer syndrome. The classic FAP phenotype is one of hundreds to thousands of adenomatous polyps in the colon, with a nearly 100% risk for developing colorectal cancer by middle age if the affected individual’s colon is not surgically removed. FAP accounts for approximately 1% of CRC cases. The incidence of FAP is approximately 1 in 10,000. While most cases arise in families with a known history through autosomal dominant inheritance, approximately 30% of cases emerge as de-novo gene mutations in the APC gene. Consequently, absence of a family history of polyposis does not exclude FAP.

**Clinical Features**

Most individuals with classic familial polyposis will develop numerous colorectal adenomas by the second or third decade of life. These adenomas are usually discovered during endoscopic evaluation for symptoms such as bleeding or diarrhea, or during routine screening in individuals with a known family history of FAP. Unfortunately, affected individuals who do not undergo early endoscopic evaluation and prophylactic colectomy often present with CRC by the fifth decade of life.

More than half of individuals affected with colonic polyposis will develop adenomatous polyps in the upper gastrointestinal tract. After adenocarcinoma of the colorectum, duodenal/ampullary adenocarcinoma is the second leading cause of cancer death for FAP patients. Fundic gland polyps are common in the stomach; however these are not known to have significant potential for malignant transformation.

Extracolonic malignancies associated with FAP include papillary thyroid cancer, adrenal carcinomas, and central nervous system tumors (Turcot’s Syndrome). Children have an increased risk for developing hepatoblastomas and require screening with liver ultrasounds and serum AFP during the first 7 years of life. Intra-abdominal desmoid tumors can appear in some individuals with FAP, often arising after abdominal surgery. While not considered malignancies, desmoid tumors can result in significant morbidity when they involve the mesentery and vasculature. Other physical findings associated with FAP include the presence of extra teeth, osteomas of the jaw and skull, and epidermoid cysts. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is an ophthalmologic finding that should prompt evaluation for FAP.

**Genetics**

Most cases of FAP are caused by germline mutations in the *adenomatous polyposis coli (APC)* gene. While most individuals with *APC* gene mutations inherited them from an affected parent, approximately one third of patients with FAP have new mutations in the *APC* gene and consequently do not have a family history of the disease.

The *APC* gene functions as a tumor suppressor. Loss of *APC* function in colonic epithelial cells is the first step toward neoplastic transformation and somatic mutations in *APC* can be found in 80% of sporadic colon cancer tumors. Germ-line mutations in *APC* are believed to be 100% penetrant and result in the development of hundreds to thousands of colorectal adenomas.

Mutations in the *APC* gene are detected in >80% of patients with the classic FAP phenotype of hundreds to thousands of adenomas. Recent reports indicate that up to 30% of individuals with classic polyposis phenotypes without a detectable *APC* mutations may have homozygous mutations in *MYH*, a base excision repair gene. Cases of *MYH*-associated polyposis can present with a similar phenotype to classic *APC*-associated FAP; however with autosomal recessive pattern of inheritance.

**Clinical Management of Familial Polyposis**

Patients at risk for FAP should begin annual colorectal screening for polyps with flexible sigmoidoscopy or colonoscopy by age 11. Most affected individuals will develop colorectal adenomas during their teenage years or early twenties. Once colorectal adenomas are too numerous to be removed endoscopically, surgical removal of the colon is required. Total proctocolectomy with ileoanal anastomosis is the preferred operation. Other less-extensive surgeries, such as total colectomy with ileorectal anastomosis, leave some colonic mucosa behind which is at risk for neoplastic transformation and requires frequent endoscopies or use of chemopreventive agents (such as COX-2 inhibitors or sulindac) to control the growth of polyps.

Once patients are found to have colorectal adenomas, upper endoscopy is recommended to assess for adenomas in the duodenum and ampulla. A sideviewing upper endoscope should be used to examine the ampulla and perform biopsies. Duodenal or ampullary adenomas can be managed through endoscopic resection or medications (COX-2 inhibitors, sulin-
dac) to reduce polyp burden. In rare cases there is extensive adenomatous involvement, severe dysplasia, or adenocarcinoma which requires surgical resection of the duodenum.

Patients with FAP are at increased risk for papillary thyroid cancer and some guidelines recommend screening with annual thyroid exams and/or thyroid ultrasounds.

Family members of individuals with FAP should be offered genetic testing for the gene mutation identified in the family in order to stratify their risk. In cases in which an individual does not undergo genetic testing or a genetic mutation cannot be identified in the family, at-risk family members should undergo colorectal screening with flexible sigmoidoscopy or colonoscopy every 1-2 years starting at age 11.

Clinical Genetic Testing
Genetic testing is now part of standard of care for risk stratification of family members of patients with a clinical diagnosis of FAP. Genetic evaluation should start with the proband with the polyposis phenotype, and should begin with testing for mutations in the APC gene. Full gene sequencing tests identify APC gene mutations in >80% of patients with classic polyposis phenotypes. If an APC mutation is not identified, then testing for biallelic mutations in the MYH gene may be considered. At present, Y165C and G382D are the two most common mutations in the MYH gene and full gene sequencing of MYH is performed in individuals who are found to have one of these 2 mutations. In cases of patients with classic polyposis in whom genetic testing for APC and MYH fails to identify a genetic mutation, all family members must be considered at risk for developing FAP and should undergo colorectal screening as described above.

Multiple Adenomas or Attenuated Adenomatous Polyposis
Individuals with 10-100 colorectal adenomas are considered to have a phenotype of multiple or attenuated polyposis. There is marked phenotypic and genotypic heterogeneity among patients with attenuated polyposis and estimates of the risk of CRC vary widely, ranging from 2x above population risk to as high as 80% for some patients. Some individuals with APC gene mutations in the 3’ or 5’ ends of the gene or with biallelic MYH mutations present with an attenuated polyposis phenotype, rather than with classic FAP. Current practice guidelines recommend genetic evaluation for patients with >20 colorectal adenomas. Cancer prevention in patients with attenuated polyposis focuses on frequent endoscopic surveillance with polypectomies to clear the colonic mucosa of adenomas; if adenomas are too numerous or recur too quickly to be managed endoscopically, then surgical colectomy may be indicated.

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