CLINICAL MANAGEMENT

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Colorectal Cancer at a Young Age

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Clinical Case

A 22-year-old man is diagnosed with stage IV poorly differentiated adenocarcinoma of the cecum with metastases to liver. There is no family history of colorectal cancer. Soon after diagnosis both parents undergo colonoscopy. His 46-year-old mother is found to have a 12-mm tubulovillous adenoma of the ascending colon that is removed during the procedure. The referring physician wonders if the patient has hereditary nonpolyposis colorectal cancer and requests a consultation regarding cancer surveillance recommendations for family members, and whether genetic testing should be performed.

Background

Clinical Features of Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer (HNPCC), also called the Lynch syndrome after Henry Lynch, MD, a pioneer in the field, carries a lifetime risk for colorectal cancer of 60%–90% and a lifetime risk for endometrial cancer of 20%–60%.[1–5] The mean age at onset of colorectal cancer in HNPCC is between 40 and 45 years, with 5% of cases occurring before 25 years of age. The risk for a number of other cancers is increased unequivocally in patients with HNPCC: most importantly, gastric, ovarian, and urinary tract cancers.[1–5] Individuals with HNPCC are at increased risk for having multiple cancers.[6] Much of the data on cancer risk, however, are not population based, and therefore may be inflated because of bias.[7]

Colorectal cancer in HNPCC differs from sporadic colorectal cancer. HNPCC-related colorectal cancers may be more likely to be proximal to the splenic flexure,[8] although recent studies have questioned this conclusion.[9] HNPCC-related cancers are more likely to have unusual histologic features (see later).[10,11] Although several studies have found that survival is better in HNPCC-related cancer compared with sporadic colorectal cancer, even when matched for stage,[12–14] larger population-based studies have not reached this conclusion.[15–17]

The colorectal adenoma is the precursor of invasive cancer in HNPCC. HNPCC-related adenomas do not clearly occur more commonly than sporadic adenomas, but they occur at a younger age, are more often in the proximal colon, are more often highly dysplastic, and are more likely to transform into cancer.[18–20]

Genetics of HNPCC

The term HNPCC originally was applied to families who met clinical criteria suggestive of an autosomal-dominant cancer susceptibility syndrome. The majority of such cases are caused by an inherited or spontaneous germline mutation in one of a set of genes responsible for DNA mismatch repair. A smaller number of families who meet clinical criteria for HNPCC have no evidence of deficient mismatch repair. The clinical and pathologic features of these families are unlike those with classic HNPCC. Most experts would no longer apply the term HNPCC to describe these families. Therefore, the term HNPCC has evolved to mean the hereditary deficient mismatch repair syndrome.

Among those with hereditary deficient mismatch repair, 90% of mutations occur in *MSH2* and *MLH1*,[21] and 5%–10% occur in *MSH6*.[22] An updated list of known mutations is available at http://www.nfdht.nl/database/mdbchoice.htm.

Abbreviations used in this paper: HNPCC, hereditary nonpolyposis colorectal cancer; IHC, immunohistochemistry; MSI, microsatellite instability; MSI-H, microsatellite instability-high.

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Persons with HNPCC have a nonfunctioning copy of one of the mismatch repair genes in the germline. When the remaining working copy of the gene is inactivated, a cell loses the ability to repair mismatches of DNA single-base pairs and short insertion and deletion loops that occur during DNA replication. Particularly vulnerable to mutation when the mismatch repair system is compromised are DNA regions in which nucleotide bases are repeated several or many times (most commonly A_n/T_n or CA_n/GT_n), termed *microsatellites*. Microsatellite instability (MSI) can be assessed from DNA extracted from a tumor in a simple assay, and is classified as being absent (microsatellite stable), low, or high (MSI-H) depending on the frequency of mutation using a standard set of 5 markers.[23] More than 90%–95% of HNPCC-related colorectal cancers are MSI-H.[24] Approximately 10%–20% of sporadic colorectal cancers are also MSI-H, almost exclusively owing to somatic inactivation of *MLH1* via promoter methylation.[25,26] Therefore, the finding of an MSI-H tumor can be suggestive, but not diagnostic, of HNPCC.[27]

Tumors that have lost the function of one of the mismatch repair genes, because of a germline mutation or somatic inactivation, usually lose expression for the protein product of that gene in the tumor, and this can be assessed by immunohistochemistry (IHC).[24]

Genotype-Phenotype Correlations in HNPCC

Extracolonic tumors are more common among *MSH2* than *MLH1* mutation carriers.[28,29] Families with *MSH6* mutations tend to have a later age of onset and a lower percentage of gene carriers developing colorectal cancer, and an abundance of endometrial cancers.[20,30]

Prevalence of HNPCC

Five population-based studies from Europe and the United States have determined that the prevalence of genetically defined HNPCC among patients diagnosed with colorectal cancer ranges between .3% and 3.4%.[31–35] Although these studies may have underestimated the prevalence of HNPCC for several reasons, it is unlikely that the burden of HNPCC among colorectal cancer patients exceeds 5%.

Potential Management Strategies

The central management questions in this case are whether or not, based on the clinical features, the diagnosis of HNPCC should be suspected and, if so, whether and how to proceed with the genetic evaluation.

Do Not Undertake Genetic Evaluation

A number of diagnostic criteria and guidelines for HNPCC have been promulgated (Table 1). All of the clinical criteria emphasize the importance of the family history of cancer. Patient-reported family cancer histories appear to be accurate and valuable for colon cancer risk assessments.[36] The data on the sensitivity and specificity of clinicopathologic criteria for the genetic diagnosis of HNPCC are problematic because most were generated in high-risk registry-based referral populations, so the broad applicability is questionable. Nevertheless, they remain the best available tools in the diagnosis of HNPCC.

The first and most stringent criteria, the Amsterdam criteria,[37] recognized that most HNPCC families are characterized by the occurrence of colorectal cancer in multiple family members, across more than one generation, and often at an early age of onset. This case meets neither the Amsterdam criteria, nor the somewhat more relaxed Amsterdam II criteria,[38] and use of these diagnostic criteria would not lead one to suspect HNPCC or undertake genetic evaluation.

Amsterdam I and II criteria perform reasonably well with respect to sensitivity and specificity for the detection of HNPCC gene carriers. When applied to registry-based populations that contain high rates of mutation-positive families, the sensitivity of the Amsterdam criteria for a genetic mutation ranges from 54% to 91%, and specificity ranges from 62% to 84%.[39] The use of Amsterdam II criteria will enhance sensitivity slightly, with a small decrease in specificity. In 2 recent studies of high-risk families, the sensitivity of the Amsterdam II criteria was 78%, with a specificity of 61%[40] and 69%, respectively.[9]

Beyond issues regarding the likelihood of making a genetic diagnosis of HNPCC in this case, genetic evaluation under any circumstance can be costly, and there are risks involved. Fear of genetic discrimination with regard to insurance and employment is a major concern to many patients who are considering genetic testing for HNPCC.[41,42] No reliable data exist on the occurrence of genetic discrimination in HNPCC. A survey of a small number of insurance providers indicated that nearly all would be willing to provide health insurance to HNPCC gene carriers, and that a majority would be willing to provide life or disability insurance.[43] The Health Insurance Portability and Accountability Act of 1996 prohibits employers or insurers from excluding individuals from group health plans or charging them higher premiums based on genetic information. In the past year the US Senate passed the Genetic Information Nondiscrim-