Colorectal Cancer: Diagnosis in a Young Adult

Posted 1-20-05

Key Points

- An early diagnosis of colorectal cancer is a possible indicator of an inherited colorectal cancer syndrome.Confirmation of an inherited colorectal cancer syndrome has implications for ongoing management of the patient and for cancer risk in biological relatives.

Learning Objectives

Participants will be able to:

- Understand the family history characteristics associated with inherited colorectal cancer syndromes;
- Understand the approach to evaluating family members for inherited risk.

Overview of Genetics of Colorectal Cancer 

Family History Issues

Some family history characteristics raise the possibility of an inherited colorectal cancer syndrome associated with high lifetime cancer risks. These characteristics include:

- Two or more relatives with CRC in the same biological line
- Relatives with CRC before age 50
- Relatives with other cancers associated with CRC, including endometrial cancer, other gastrointestinal cancers, urinary tract cancers, and ovarian cancer

Red Flags 

Inherited CRC risk should be suspected if:

- CRC occurs before age 50;
- Multiple colonic polyps are noted on endoscopy;
- Two primary colon cancers occur in the same individual;
- CRC and another associated cancer (endometrial cancer, other gastrointestinal cancers, urinary tract cancers, and ovarian cancer) occur in the same individual.

Case 9. Colorectal Cancer in a 28-Year-Old Woman

A resident presents a new patient, referred by the gastroenterology service. She is a 28-year-old woman who recently underwent a subtotal colectomy for right-sided colorectal cancer (CRC). Her presenting symptom was lightheadedness secondary to anemia, which is now corrected. The tumor was contained within the wall of the colon and no additional cancer therapy was recommended. She is otherwise in good health. The gastroenterology service will see her annually for surveillance of the remaining rectal tissue.

Clinical Care Issues

This patient may benefit from supportive counseling related to her recent and probably unexpected colon cancer diagnosis. She may have questions related to lifestyle issues, such as appropriate exercise and eating program following surgery. Depending on her life circumstances, she may want to discuss reproductive options. Other routine health maintenance may also be due. Most important, however, her early age of diagnosis suggests she may have an inherited CRC syndrome; if so, her medical care should include consideration of other cancer risks. In addition, family members may be at risk.

Risk Assessment

Relevant risk factors

By virtue of her very early age of onset, this patient is likely to have an inherited predisposition to CRC, unless she has had a long history of inflammatory bowel disease preceding the colon cancer diagnosis. Identification of the inherited syndrome will provide information about other health risks for the patient, and will also provide risk information for her

relatives.

Role of family history in assessing risk

A family history of CRC and related cancers can confirm inherited risk in this patient. Relevant family history includes:

- Two or more relatives with CRC
- Sequential generations affected
- One or more family members affected at an early age (i.e., before age 50 years)
- Other cancers that are associated with inherited colorectal cancer, most commonly endometrial cancer, but also including cancer of the stomach, ovary, hepatobiliary tract, small bowel, urinary tract, brain/CNS
- Multiple primary tumors in a single individual (e.g., two or more colorectal neoplasms or CRC in combination with endometrial or other associated cancer)

What inherited syndromes might account for this risk?

Two rare conditions account for most inherited CRC: Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colon Cancer (HNPCC).

Genetic Counseling and Testing

The first step in genetic counseling for this patient would be a review of pathology reports from surgery for evidence concerning the possibility of familial adenomatous polyposis (FAP). If the pathology examination of the resected colon revealed numerous colon polyps (≥100), this finding would indicate a diagnosis of FAP. A moderate number of polyps (average of 30) would suggest attenuated FAP (AFAP) [Knudsen et al 2003]. If FAP is ruled out, the next step is a careful assessment of the patient's family history for evidence of HNPCC.

If family history is unknown or ambiguous, further testing may help to confirm the suspected diagnosis of HNPCC. The usual approach in this case is to test the tumor tissue for microsatellite instability (MSI) and/or for presence of the MSH2 and MLH1 proteins using immunohistochemistry. If either of these tests is positive, DNA-based testing could be done on a blood sample to search for a causative mutation that would confirm HNPCC.

HNPCC is caused by a mutation in one of four genes (*MSH2, MLH1, MSH6, PMS2*), all involving DNA repair functions known as "mismatch repair" — that is, genes that code for proteins involved in repairing DNA replication errors that occur during cell division. Genetic testing is currently available for mutations in *MSH2*, *MLH1*, and *MSH6*. The sensitivity of the testing is estimated to be 60-70%; that is, only 60-70% of people with a clinical diagnosis of HNPCC (based on the presence of cancer and a diagnostic family history) have an identifiable causative mutation.

If the patient's family history meets the modified Amsterdam criteria for HNPCC, genetic testing is not necessary to confirm the diagnosis.

Modified Amsterdam criteria for HNPCC

- Two or more other relatives — total of at least three in family — have HNPCC-associated cancer (colorectal cancer or cancer of the endometrium, stomach, ovary, hepatobiliary tract, small bowel, urinary tract, brain/CNS); AND
- All of the following:
  - One affected relative is a first-degree relative of the other two;
  - Two or more successive generations are affected;
  - At least one relative had colorectal cancer before age 50;
  - FAP has been excluded.

Genetic testing can also provide information to family members about their risk. If a causative mutation is found, genetic testing can be used to identify healthy family members who have inherited the cancer-predisposing mutation and thus may benefit from early and intensive colorectal cancer screening. For those who have not inherited the cancer-predisposing mutation present in the family, routine CRC screening can be offered. This risk information may also be helpful to family members in making other life decisions.

Optimal testing strategy

An important caveat about genetic testing for inherited HNPCC-related mutations is limited sensitivity: cancer-predisposing mutations can be found in only about 60-70% of affected families. Therefore, the optimal testing strategy is as follows:

1. Test affected relative first. In this case, the patient would be the appropriate person to test.
2. If a mutation is identified, testing for this mutation can be offered to asymptomatic at-risk relatives to determine if they have inherited the mutation and therefore the cancer predisposition.
3. If no mutation is identified in an affected individual, testing for family members is deemed "uninformative." In that case, all at-risk individuals in the family need to continue CRC screening appropriate to high-risk individuals (colonoscopy every one to two years, starting at age 20-25 or ten years before the earliest diagnosis in the family) because genetic testing cannot determine who has inherited a cancer-predisposing mutation and who has not.

Interventions

Assuming that her family history confirms HNPCC, this patient's care can be determined by her clinical status and her family history. Specifically, she is a candidate for ongoing surveillance of the remaining rectal tissue, because of her early cancer diagnosis. She should also be considered for endometrial and ovarian cancer screening, and some experts recommend screening with upper endoscopy and urine cytology (see *GeneReview*: HNPCC, Management).

Ethical/Legal/Social/Cultural Issues

Distress and discrimination

Genetic testing involves potential risks as well as benefits. Knowledge of an inherited predisposition may cause anxiety, guilt, and family distress, and may also pose a risk of stigmatization and discrimination in access to insurance or employment [Hudson et al 1995, Rothenberg 1995]. Appropriate protection of privacy must be considered. There is expert consensus that individuals contemplating genetic testing should have pre-test counseling to ensure the opportunity to consider these issues prior to making a decision, and post-test counseling, to ensure that the results are understood [Geller et al 1997]. However, few studies have assessed the efficacy of genetic counseling, and the scope of personal and social risks posed by genetic testing has not been studied systematically.

"Duty to warn"

Some case law raises the question of a physician's "duty to warn" family members of their risk for an inherited cancer risk [Offit et al 2004]. In one commonly cited case, a daughter affected with FAP sued the estate of her father's physician, claiming the doctor should have informed her of her father's FAP diagnosis and her own risk. The case was settled out of court, and the issue remains controversial [Safer v Pack 1996]. A recent statement by the American Society of Clinical Oncology [ASCO 2003] proposes that the duty of the physician caring for a patient with an inherited cancer syndrome is limited to informing the patient of the inherited nature of the condition and the risk to family members.

Resources

- **Hereditary Colon Cancer Association (HCCA)**
  3601 N 4th Ave, Suite 201
  Sioux Falls, SD 57104
  Phone: 800-264-6783; 605-373-2067
  Fax: 605-336-6699
  Email: info@hereditarycc.org

- **Colorectal Cancer Network**

- **Cancer.gov - Colon and Rectal Cancer: Prevention, Genetics, Causes**

- **Cancer.gov - Colorectal Cancer (PDQ): Prevention**

- **Johns Hopkins Hereditary Colon Cancer Web site**

- **GeneTests Online Medical Genetics Information Resource**

- ***GeneReview:* Familial Adenomatous Polyposis**

- ***GeneReview:* Hereditary Nonpolyposis Colon Cancer**

References

American Society of Clinical Oncology (2003) Policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 21:2397-406 [Medline]

Geller G, Botkin JR, Green MJ, Press N, Biesecker BB, Wilfond B, Grana G, Daly MB, Schneider K, Kahn MJ (1997) Genetic testing for susceptibility to adult-onset cancer: the process and content of informed consent. *JAMA* 277:1467-74 [Medline]

Hudson KL, Rothenberg KH, Andrews LB, Kahn MJ, Collins FS (1995) Genetic discrimination and health insurance: an urgent need for reform. *Science* 270:391-3 [Medline]

Knudsen AL, Bisgaard ML, Bulow S (2003) Attenuated familial adenomatous polyposis (AFAP). A review of the literature. *Fam Cancer* 2:43-55 [Medline]

Lipton LR, Johnson V, Cummings C, Fisher S, Risby P, Eftekhar Sadat AT, Cranston T, Izatt L, Sasieni P, Hodgson SV, Thomas HJ, Tomlinson IP (2004) Refining the Amsterdam Criteria and Bethesda Guidelines: testing algorithms for the prediction of mismatch repair mutation status in the familial cancer clinic. *J Clin Oncol* 22:4934-43 [Medline]

New Jersey. Superior Court, Appellate Division (1996) Safer v Estate of Pack. *Atl Report* 677:1188-93 [Medline]

Offit K, Groeger E, Turner S, Wadsworth EA, Weiser MA (2004) The "duty to warn" a patient's family members about hereditary disease risks. *JAMA* 292:1469-73 [Medline]

Rothenberg KH (1995) Genetic information and health insurance: state legislative approaches. *J Law Med Ethics* 23:312-9 [Medline]

Smith RA, von Eschenbach AC, Wender R, Levin B, Byers T, Rothenberger D, Brooks D, Creasman W, Cohen C, Runowicz C, Saslow D, Cokkinides V, Eyre H; ACS Prostate Cancer Advisory Committee, ACS Colorectal Cancer Advisory Committee, ACS Endometrial Cancer Advisory Committee (2001) American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001--testing for early lung cancer detection. *CA Cancer J Clin* 51:38-75; quiz 77-80 [Medline]

Vasen HF, Watson P, Mecklin JP, Lynch HT (1999) New clinical criteria for hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 116:1453-6 [Medline]

Winawer SJ, Fletcher RH, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C; Gastrointestinal Consortium Panel (2003) Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. *Gastroenterology* 124:544-60 [Medline]