CLINICAL CASE OF THE MONTH

A 62-Year-Old Man Presenting with Shortness of Breath for 6 Months

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A 62-year-old man with no significant past medical history presented to the emergency department with a chief complaint of shortness of breath for 6 months. The patient stated that at baseline he experienced shortness of breath after walking approximately 100 feet, but that this progressively worsened over the course of six months until the morning of presentation when he was unable to get out of bed as a result of his shortness of breath. He also noted occasional dark maroon stools during this time. The patient also complained of intermittent nonbloody diarrhea and dull abdominal pain during the same period. He denied nausea, vomiting, constipation, or hematemesis. He also denied any recent illness, fever, chills, or sick contacts, any history of cardiac or renal disease, and any history of peptic ulcer disease, upper GI bleeding, or symptoms of gastroesophageal reflux. He had no history of having undergone an endoscopy or colonoscopy.

The patient denied any significant past medical history, past surgical history, or family medical history. The patient denied the use of any medications, and had no known allergies. He had a 30-pack-year history of smoking, but he quit 7 months prior to presentation. He also admitted to a 30-year-history of alcohol use (approximately three to four beers per day), which he discontinued 10 years ago. The patient denied any history of illicit drug use.

Vital signs at admission included a temperature of 96°F, pulse of 96 beats per minute, respiratory rate of 16/minute, blood pressure of 117/70 mmHg, and an oxygen saturation of 98% on room air. The patient was alert, oriented, and cooperative with the interview and examination, and was in no apparent distress. The patient had anicteric sclerae, and examination of the head, eyes, ears, nose and throat was unremarkable. The neck was supple and without masses or lymphadenopathy. The cardiovascular exam revealed no abnormalities, and the patient's lungs were clear to auscultation bilaterally. The abdomen was nondistended, soft, and nontender, with normoactive bowel sounds. No hepatosplenomegaly was appreciated, and there were no palpable masses. Stool examination was strongly heme-positive, and there were no masses or hemorrhoids present. Examination of the patient's extremities was unremarkable.
Serum chemistries on presentation demonstrated a sodium of 135 mmol/L (normal range, 135-146 mmol/L), potassium of 4.2 mmol/L (normal range, 3.6-5.2 mmol/L), chloride of 105 mmol/L (normal range, 96-107 mmol/L), bicarbonate of 25 mmol/L (normal range, 24-32 mmol/L), blood urea nitrogen of 12 mg/dL (normal range, 7-25 mg/dL), creatinine of 0.9 mg/dL (normal range, 0.8-1.6 mg/dL), glucose of 94 mg/dL (normal range, 65-99 mg/dL), and calcium of 8.9 mg/dL (normal range, 8.4-10.3 mg/dL). Liver panel revealed an albumin of 4.0 gm/dL (normal range, 3.5-5.0 gm/dL), total protein of 7.8 gm/dL (normal range, 6.0-8.0 gm/dL), total bilirubin of 0.2 mg/dL (normal range, <1.3 mg/dL), AST of 20 U/L (normal range, <45 U/L), ALT of 15 U/L (normal range, <46 U/L), alkaline phosphatase of 131 U/L (normal range, 20-131 U/L). Cardiac enzymes were unremarkable. The patient’s blood count revealed a white blood count of 8.3 x 10^3/μL (normal range, 4.5-11.0 x 10^3/μL), hemoglobin of 4.4 gm/dL (normal range, 13.5-17.5 gm/dL), hematocrit of 14.4% (normal range, 40-51%), platelet count of 607 x 10^3/μL (normal range, 103-400 x 10^3/μL), mean corpuscular volume of 65.2 FL (normal range, 80-100 FL), and RDW of 23.4% (normal range, 11.5-14.5%). The patient’s iron studies revealed a serum iron level of 9 ug/dL (normal range, 50-170 ug/dL), transferrin of 296 mg/dL (normal range, 200-360 mg/dL), total iron binding capacity of 385 ug/dL (normal range, 250-425 ug/dL), and ferritin of 6.4 ng/mL (normal range, 20.0-300.0 ng/mL).

The patient received packed red blood cells for management of his symptomatic iron deficiency anemia. He underwent endoscopy which revealed a solitary submucosal nodular lesion in the lower esophagus which was biopsied and eventually discovered to be a focal area of acute inflammation. Colonoscopy revealed old blood throughout the distal colon (without any masses or polyps noted), but a large, hemorrhagic, fungating, circumferential mass was noted in the proximal colon at approximately 90 cm of scope length. Multiple biopsies were obtained and revealed invasive poorly differentiated carcinoma suggestive of adenocarcinoma (Figure 1).

Computed Tomographic (CT) scans of the abdomen and pelvis were subsequently performed and revealed the large mass in the proximal colon (Figure 2), as well as pericolonic expansion and bowel wall thickening. In addition, a large 4.5 cm right hepatic lobe mass (Figure 3) consistent with metastatic disease was appreciated. Tumor cells were noted in the deeper mucosal layers.
Upon measurement, CEA level was noted to be 1.1 ng/mL (normal range, <3 ng/mL).

The patient underwent a right hemicolectomy and liver biopsy. Pathologic analysis of colonic specimens revealed clean margins surrounding the resected mass which proved to be an invasive poorly differentiated adenocarcinoma. Liver biopsy (Figure 4) revealed necrosis with infiltrating poorly differentiated adenocarcinoma (consistent with metastasis), and two of seven lymph nodes were positive for metastatic cancer. The patient had no complications following surgery and was discharged with plans for care that included chemotherapy.

DISCUSSION

While the goal of screening for CRC is to diagnose asymptomatic patients with premalignant lesions, the majority of patients diagnosed with CRC are in fact symptomatic. The types of symptoms are often dependent on the location of the tumor. Patients with right-sided colon cancer tend to have constitutional symptoms such as weakness, fatigue, weight loss, and dyspnea on exertion due to a microcytic hypochromic anemia. This presentation is ascribed to the larger luminal size of the cecum and ascending colon allowing the tumor to attain a larger size before obstructive symptoms are apparent. In contrast, left-sided lesions involving the descending and sigmoid colon often present with symptoms reflective of the smaller lumen. “Colicky” abdominal pain from partial obstruction or distention is a frequent presentation. Additionally, a change in bowel habits where constipation may alternate with frequent bowel movements is ascribed to small amounts of stool moving beyond the obstructive lesion.3 Hematochezia or bright red blood per rectum is also more common with lesions involving the distal left colon and rectum. Unusual presentations of CRC include local invasion into adjacent organs, fever of unknown origin, Streptococcus bovis bacteremia, or Clostridium septicum sepsis.

PATHOGENESIS

Most colorectal cancers arise from colonic polyps, which may be adenomatous or hyperplastic. Biopsy and histologic evaluation are necessary to differentiate these two types of polyps. While hyperplastic polyps are not generally considered to carry an increased risk for development of CRC, adenomatous polyps do carry this risk.4 The incidence of adenomas increases with age, and approximately 25% of the population will have adenoma(s) by age 50. Polyps usually exhibit a progression from smaller to larger size and from dysplasia to carcinoma, a process which usually takes about 10 years.5 Typically, the chances of detected polyps becoming dysplastic or cancerous vary with size, number of polyps, and histologic architecture.6 Large, flat polyps (>1 cm) are more worrisome than smaller ones because they are more likely to become dysplastic. Likewise, polyps with villous architecture are more concerning than those with tubular architecture, and greater numbers of polyps are associated with an increased risk of dysplasia and/or carcinoma.

Removal of worrisome lesions confers a morbidity advantage. In a study of 1418 patients who underwent complete colonoscopy during which one or more polyps were removed, six-year follow-up demonstrated an incidence of CRC that was approximately 90% lower than in patients who had not undergone polypectomy, and 76% lower than that of the general population.7
RISK FACTORS

While CRC is an acquired condition, there are genetic factors that contribute to the risk of developing CRC. There is a positive family history of CRC in 10% of adults in the general population, and in 25% of patients with CRC. Certain conditions which are known to be inherited may increase the risk of CRC in some patients. Physicians should attempt to assess a patient’s risk of CRC by inquiring about a family history of CRC, especially with regard to first degree relatives, a personal history of CRC or polyps, and a history of inflammatory bowel disease (IBD). Patients who meet any of these criteria are considered to be at increased risk for the development of CRC, while those who do not are considered to be at average risk.

Genetic conditions associated with increased risk of CRC include Hereditary Nonpolyposis Colorectal Cancer (HNPPC or Lynch Syndrome) and Familial Adenomatous Polyposis (FAP). HNPPC, an autosomal dominant condition which confers a 70% risk of developing CRC, represents about 2 to 5% of all cases of CRC. In addition, patients with HNPPC are generally diagnosed with CRC in the 3rd or 4th decade of life, whereas others are usually diagnosed after the age of 50. Colorectal cancers associated with HNPPC tend to occur more often in the proximal colon. HNPPC does not result in a higher frequency of adenomatous polyps, however, FAP, another autosomal dominant condition, does. FAP represents about 1% of all cases of CRC, and manifests itself as hundreds of polyps throughout the colon. It carries a risk of CRC that approaches 100% and can have an onset as early as adolescence.

Further elements of the patient’s past medical history that are of concern include prior polyps and prior history of CRC, which confers a twofold increase in risk for development of CRC in a second site. Patients with a history of IBD are also at increased risk for developing CRC, especially if the disease has been present for several years. Other risk factors for CRC include sedentary lifestyle, excessive intake of red meat, obesity, tobacco, and alcohol use. Some possible protective factors include NSAID use, high fiber diet, postmenopausal hormone replacement therapy, and adequate supplementation of folate, calcium, and selenium, although it is generally agreed that further study designed to characterize the protective effects of these agents is necessary.

SCREENING

Several options for CRC screening currently exist; however, there is much debate as to which screening protocol is the most cost effective. Several different modalities, including fecal occult blood testing (FOBT), flexible sigmoidoscopy, colonoscopy, and double contrast barium enema are currently among the acceptable screening tests, although the optimal intervals for administration of these various screening tests is still being studied. Though it is unnecessary to repeat tests such as colonoscopy and flexible sigmoidoscopy annually, there is an advantage to yearly administration of less sensitive tests, such as FOBT, in that previously undetected lesions may be discovered. Procedures such as colonoscopy and flexible sigmoidoscopy, which allow for direct visualization of the colon, may actually reduce the mortality rate secondary to CRC in that they enable the endoscopist to remove precancerous polyps (thus decreasing the incidence of CRC) or remove actual cancers to confer a prognostic advantage.

The first clinical trial that evaluated FOBT as a screening modality demonstrated that the 13-year cumulative mortality from CRC could be reduced by 33% with annual FOBT testing if positive tests were followed by colonoscopy. It has also been demonstrated that annual FOBT, in addition to decreasing the mortality due to CRC, can also significantly reduce the incidence of CRC. Disadvantages of FOBT include a high false-positive rate which leads to unnecessary colonoscopies and a markedly decreased sensitivity (from 90% to less than 50%) if the test is not administered annually. Thus, the combination of FOBT with another screening modality would likely be more beneficial than the use of FOBT alone.

Sigmoidoscopy allows for direct visualization of the colon up to the splenic flexure (approximately 60 cm), and affords the endoscopist the opportunity to take biopsies of lesions that may be detected. Sigmoidoscopy as a screening tool can reduce the mortality due to CRC by two-thirds in the part of the colon examined. The recommended interval for follow up sigmoidoscopy after a normal exam is 5 years, while abnormal exams should be followed with colonoscopy. For patients who have only a single small distal tubular adenoma, it is acceptable to offer colonoscopy or to treat these patients as average risk.

The obvious limitation of sigmoidoscopy is the length of the sigmoidoscope. Since it reaches only about one-half of the colon, any lesions that may be present in the proximal part will be missed. Indeed, it is estimated that an additional 20% of neoplasms would be found if abnormal sigmoidoscopies were followed by colonoscopy. One way to increase the yield of this test is to combine sigmoidoscopy every five years with annual FOBT. While there are no direct studies to evaluate the efficacy of this regimen, it has been shown that sigmoidoscopy in combination with one-time FOBT increased the detection rate of colonic neoplasia from 70% to 76%. Since a positive FOBT warrants colonoscopy, the FOBT test should be performed first when using the combined screening regimen of FOBT and sigmoidoscopy.

Colonoscopy, which is considered by the American College of Gastroenterology (ACG) to be the preferred screening tool, confers several advantages over FOBT and sigmoidoscopy. There has been much argument support-
Colonoscopy enables the physician to visualize almost all lesions and allows for excision of most lesions at the time of endoscopy, a luxury that sigmoidoscopy does not afford. The colonoscope also finds lesions missed by the sigmoidoscope, especially proximal colonic lesions which previously may not have been reached and visualized. Disadvantages of colonoscopy include an increased risk of perforation, higher cost, and necessity of a good bowel prep prior to the procedure.

Double contrast barium enema (DCBE) also requires a bowel prep, but unlike colonoscopy, there is no sedation required for the exam. DCBE detects only 50% of polyps greater than 1 cm and 39% of all polyps. Radiologic artifacts resulting from retained stool, air, or mucosal irregularity contribute to the high false-positive rate associated with DCBE. There are currently no randomized trials which target the effect of DCBE on incidence of CRC or resultant mortality. Other screening modalities which are currently under investigation include testing for fecal genetic abnormalities, pill capsule endoscopy, and virtual colonoscopy.

The most commonly used screening protocol for patients at average risk for CRC is annual FOBT with flexible sigmoidoscopy every 5 years; however, colonoscopy at 10-year intervals is preferred by the ACG. Current recommendations are to begin screening these individuals at age 50. It is also recommended that any positive FOBT or discovery of adenomas via endoscopy be followed by colonoscopy to rule out pathologic conditions of the proximal colon.

For patients at an increased risk, recommendations are more complex, and the evidence supporting the different protocols is not as strong. For patients with first degree relatives with a history of CRC or adenomas diagnosed before age 60, screening with colonoscopy should be offered at age 40, or 10 years prior to the age of the family member at the time of diagnosis, whichever is sooner. In addition, screening colonoscopy in these patients should be conducted at more frequent intervals than in average risk patients (i.e., every 5 years instead of every 10). If the family member was diagnosed after the age of 60, then the patient may be screened every 10 years, but screening should start at age 40 instead of 50. For patients with a family history of FAP, genetic testing is recommended. Patients in whom the presence of the FAP gene cannot be ruled out should be screened with flexible sigmoidoscopy each year beginning in adolescence. Flexible sigmoidoscopy is acceptable in these patients, because in FAP, polyps will occur in the entire colon. Patients with a family history suggestive of HNPCC should be offered genetic counseling, as well as colonoscopy every 1 to 2 years beginning between 20 and 30 years of age, and annually after 40 years of age. In these patients, colonoscopy should be used instead of flexible sigmoidoscopy because distal polyps may or may not be present.

**DIAGNOSIS**

Once a detailed history and physical examination reveals a clinical suspicion for CRC, the procedure of choice is colonoscopy. The majority of colorectal cancers are intraluminal adenocarcinomas which arise from the mucosa. Thus, colonoscopy offers the ability to localize lesions in the large bowel, as well as the capability to biopsy or remove lesions for histological evaluation. In the small percentage of patients in which colonoscopy is unable to be completed because of technical reasons, there are alternatives, including DCBE, pill-capsule endoscopy, and virtual colonoscopy using CT.

A number of serological markers have been investigated for both detection and surveillance of CRC. To date, none have proven to be effective for screening patients because of their low sensitivity and specificity in asymptomatic patients. The most widely used and studied serum tumor marker is carcinoembryonic antigen (CEA). After CRC has been diagnosed by more conventional methods, CEA levels are typically used in the preoperative staging and postoperative follow up as a marker for residual or recurrent disease. One limitation of CEA as a tumor marker is that it is usually elevated late in the course of CRC, so it is not very effective for screening patients with suspected early disease. Since CEA may not always be elevated in patients with CRC, direct visualization of the colon via endoscopy remains the diagnostic tool of choice.

**TREATMENT**

The treatment of choice for CRC is surgical resection with or without adjuvant chemotherapy. Surgical resection of CRC is usually guided by the vascular supply and requires an adequate margin of resection, usually defined as 5 cm of normal bowel on each side of the lesion. Furthermore, a wider resection is usually required to achieve sufficient lymph node sampling which is important in determining both treatment and prognosis. Right-sided lesions (i.e., those involving the cecum and ascending colon) will usually require a right hemicolecctiony. Tumors in the mid-transverse colon can be resected from the hepatic flexure to the splenic flexure. Lesions in the descending and sigmoid colon can be removed via segmental resection with primary anastomosis. Finally, rectal cancers can be resected utilizing a lower anterior resection with primary anastomosis. However, if an adequate margin (usually 2 cm) cannot be obtained, then an abdominoperineal resection with ileostomy may be necessary. In addition to the primary tumor, metastatic
liver lesions are discovered at the time of surgery in as many as 10 to 25% of patients. Liver lesions may be resected for cure if no extrahepatic metastasis is present and if there is no underlying hepatic disease such as cirrhosis.23

In addition to vascular supply, another important factor that one must consider when formulating a treatment plan for these patients is the pathologic stage of the tumor. Stage 0 disease is usually defined as carcinoma in situ without invasion of the submucosa. Tumors involving the submucosa without any nodal or distant metastasis are designated as Stage I. Stage II tumors are those which invade through the muscularis propria to the subserosa and may even involve the visceral peritoneum or direct extension into adjacent organs. Finally, bowel wall perforation and regional lymph node metastasis are characteristics of Stage III disease while distant metastases are the hallmark of Stage IV disease.24

Adjuvant chemotherapy with leucovorin and 5-fluorouracil is recommended for Stage III disease, but not Stage II disease. However, it may be considered in those patients with incomplete lymph node sampling or high risk Stage II lesions (i.e., perforation, T4 lesions, poorly differentiated histology). Other chemotherapeutic regimens are also available. Radiation treatment might be helpful for patients at high risk for local recurrence (i.e., positive margins, perforation, invasion of adjacent organs) and should be considered on an individual basis.25

PROGNOSIS AND SURVEILLANCE

The most important prognostic indicator is the pathologic stage of the cancer. The 5-year survival rates for rectal cancer are as follows: Stage I (72%), Stage II (52%), Stage III (37%), and Stage IV (4%).26 The survival rates for colon cancer tend to be slightly higher: Stage I (95%), Stage II (60-80%), Stage III (40-60%), and Stage IV (4%). Other prognostic determinants include the number of regional nodal metastases (Stage III), histologic type, and microsatellite instability. Furthermore, those with lymphovascular invasion and high preoperative serum CEA levels will have poorer outcomes.27

In terms of surveillance, there is no consensus on monitoring CEA levels. Most recommendations consist of CEA levels every 2 to 3 months for at least 2 years. This can be continued every 6 months for a total of 5 years. There are no recommendations for routine complete blood counts, liver function panels, or abdominal CT scans. A surveillance colonoscopy should be done 6 months post-resection for rectal cancer, and 1 year post-resection for colon cancer. If the colonoscopy is normal, it should be repeated in 3 years and thereafter based on the regular adenoma surveillance recommendations.

REFERENCES

CME QUESTIONS

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For each question, choose the one answer that is most correct.

1. All of the following comments are correct except:
   a) Approximately 33% patients diagnosed with colorectal cancer die from complications of colorectal cancer.
   b) Patients with right-sided colon cancer tend to have constitutional symptoms such as weakness, fatigue, weight loss, and dyspnea on exertion due to a microcytic hypochromic anemia.
   c) The incidence of colon-associated adenomas decreases with age, and approximately 1% of the population will have adenoma(s) by age 50.
   d) Left-sided colorectal cancers involving the descending and sigmoid colon and often present with bright red blood per rectum and symptoms reflective of the smaller lumen, including “colicky” abdominal pain.

2. True or False? Although colorectal cancer is the third most common type of cancer in both sexes, it represents less than 1% of all cancer deaths.

3. True or False? Greater than 90% of colorectal cancer cases occur after 50 years of age.

4. All of the following statements are true except:
   a) There is a positive family history of colorectal cancer in 10% of adults in the general population, and in 25% of patients with colorectal cancer.
   b) Physicians should attempt to assess a patient’s risk of colorectal cancer by inquiring about family history of colorectal cancer, especially with regard to first degree relatives, personal history of colorectal cancer or polyps, and history of inflammatory bowel disease. Patients who meet any of these criteria are considered to be at increased risk for the development of CRC while those who do not are considered to be at average risk.
   c) Several different modalities, including fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, and double contrast barium enema, are currently among the acceptable screening tests, although the optimal intervals for administration of these various screening tests is still being studied.
   d) Sigmoidoscopy allows for direct visualization of the colon up to the splenic flexure (approximately 60 cm).
   e) Virtual colonoscopy is currently recommended as a standard screening modality for colorectal cancer.

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The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical Students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions.