50-Year-Old Woman With Fatigue

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A 50-year-old postmenopausal woman with a history of hypothyroidism and obesity presented to her primary care physician with a several-month history of fatigue. On evaluation, she had no history of fever, chills, night sweats, weight change, abdominal pain, peptic ulcer disease, hematochezia, melena, hematemesis, or hemoptysis. Her only medication was levothyroxine (one 75-μg tablet daily). She was a lifelong nonsmoker and drank no alcohol. Her family history was notable for bladder cancer in her father and gastric cancer in her maternal grandmother. Her mother had no medical problems. Her vital signs were as follows: temperature, 36.8°C; pulse rate, 90 beats/min; blood pressure, 119/68 mm Hg; height, 175.9 cm; and weight, 116.6 kg. Routine laboratory studies (reference ranges provided parenthetically) revealed low levels of hemoglobin (9.6 g/dL [12.0-15.5 g/dL]), hematocrit (30% [33.3%-43.3%), and mean corpuscular volume (72.3 fL [82.7-96.8 fL]). Serum iron studies revealed a low iron level (27 μg/dL [35-145 μg/dL), a total iron-binding capacity of 406 μg/dL (250-400 μg/dL), and a low ferritin level (7 μg/L [11-307 μg/L]).

1. Which *one* of the following is the *most appropriate* next step in the evaluation of this patient with iron deficiency anemia (IDA)?

a. Serum transferrin measurement
b. Colonoscopy
c. Serum anti—tissue transglutaminase antibody assay
d. Bone marrow aspiration and biopsy
e. No further testing is necessary

Iron deficiency anemia usually is suspected when a routine complete blood cell count indicates microcytic anemia. It is associated with low iron and ferritin levels and high total iron-binding capacity. If the diagnosis remains obscure after serum iron studies, serum transferrin measurement can assist in the diagnosis because levels are elevated in IDA and normal in anemia of chronic disease. If the patient is male or a nonmenstruating female, the initial step is endoscopic evaluation of the alimentary tract to evaluate for occult gastrointestinal bleeding. If the patient is a premenopausal female, endoscopic evaluation can be considered, but a trial of iron supplementation also is appropriate. Serum anti—tissue transglutaminase antibody measurement for celiac disease would be helpful if the patient had a history of bulky, foul-smelling stool or a previous diagnosis of irritable bowel syndrome. Bone marrow biopsy or aspiration would be appropriate if the diagnosis remained unclear. It is unnecessary in this case because serum studies established the diagnosis. The option of no further testing is inappropriate because further evaluation to determine the cause of this patient's IDA is indicated.

With the current patient, a 50-year-old postmenopausal woman with symptomatic IDA, an endoscopic evaluation was performed. Colonoscopy revealed 25 to 30 polyps in the ascending colon, approximately 4 to 5 in the transverse and descending colon, and an ulcerated polypoid mass in the cecum. Examination of a biopsy specimen revealed an invasive, moderately differentiated colon adenocarcinoma. Additional tubulovillous adenomas were removed from the right ascending, transverse, descending, and sigmoid colon, along with a tubular adenoma in the rectum, none of which had high-grade dysplasia. Upper endoscopy revealed 2 sessile polyps in the second portion of the duodenum and multiple gastric polyps in the body and fundus; examination of biopsy specimens was negative for malignant disease.

2. In view of the findings at this time, which *one* of the following is the *best* next step?

a. Whole-abdomen radiation
b. Neoadjuvant chemotherapy followed by total colectomy
c. Preoperative radiation followed by total colectomy
d. Laparoscopic total colectomy
e. Systemic chemotherapy without surgical intervention

See end of article for correct answers to questions.

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Management of colon cancer is primarily surgical. Whole-abdomen radiation is used rarely in recurrent gynecologic malignant neoplasms and does not have a role in colon cancer. Neoadjuvant chemotherapy is often used for treatment of rectal cancers but has not been proven beneficial in colonic malignant tumors. Preoperative radiation is rarely an optimal choice because radiation causes damage to surrounding tissues, making surgical resection difficult; it does not have a role in the management of colon cancer. Laparoscopic total colectomy is the best management option because of the large polyp burden, cecal cancer, and concern about a possible hereditary cancer syndrome. The decision to treat with chemotherapy after surgical intervention is based on the stage of disease. Systemic chemotherapy without surgical intervention is reserved for widespread metastatic disease, for which surgery could not offer a cure.

After laparoscopic total colectomy, pathologic examination revealed a moderately differentiated adenocarcinoma, grade 3 to 4. No lymphovascular invasion or perineural invasion was observed, surgical margins were clear, and no lymph nodes were involved. Stage IIA (T3N0M0) disease was diagnosed. Numerous polyps were found throughout the colon, with the greatest density in the ascending colon.

Adjuvant chemotherapy for stage II colon cancer remains controversial.[1] The risks and benefits of adjuvant chemotherapy should be discussed for all patients with stage II colon cancer. Current national guidelines recommend adjuvant therapy for stage II colon cancer in patients with strong risk factors for recurrence (tumor perforation, poorly differentiated histology, T4 tumors, lymphovascular invasion, perineural invasion, or <13 lymph nodes sampled).[1] Appropriate adjuvant therapy regimens include 5-fluorouracil and leucovorin, single-agent capecitabine, 5-fluorouracil–leucovorin and oxaliplatin, or capecitabine and oxaliplatin, or patients may be enrolled in a clinical trial. More recently, evidence has revealed the prognostic value of defective DNA mismatch repair (MMR) in stage II disease. Defective MMR leads to microsatellite instability, defined as mutations occurring in short repeated sequences of nucleotides located in promoter regions of regulatory genes. Tumors deficient for MMR are termed *microsatellite instability high* and are known to have a better prognosis. Patients with stage II microsatellite instability–high tumors do not benefit from 5-fluorouracil–based chemotherapy.[2]

After the operation, the patient opted to begin adjuvant chemotherapy with 5-fluorouracil and leucovorin. She also met with a genetic counselor.

3. Which *one* of the following genetic syndromes is *mostly likely* in this patient?

a. Lynch syndrome (LS)
b. Li-Fraumeni syndrome (LFS)
c. mutY human homolog (*MUTYH*) gene–associated polyposis
d. Peutz-Jeghers syndrome
e. Familial juvenile polyposis

Lynch syndrome is an autosomal dominant hereditary colon cancer syndrome, also termed *hereditary nonpolyposis colorectal cancer* because, unlike other genetic syndromes, it is not associated with polyposis. Bethesda guidelines help identify patients with increased risk of LS. The guidelines recommend genetic testing for LS in patients with (1) colorectal cancer diagnosed at age 50 years or younger, (2) synchronous or metachronous lesions or other LS-related tumors, (3) colorectal cancer with microsatellite instability–high histology at age 60 years or younger, (4) one or more first-degree relatives with LS-related cancer at age 50 years or younger, or (5) 2 or more first- or second-degree relatives with LS-related cancer.[3] Patients with colorectal cancer may be screened for LS using immunohistochemical staining for MMR proteins or by polymerase chain reaction–based testing for microsatellite instability. At the time of initial diagnosis, this patient was screened for LS; immunohistochemical staining of tumor tissue revealed normal MMR protein expression.

Li-Fraumeni syndrome is an autosomal dominant hereditary cancer syndrome caused by mutations in the *TP53* gene. With loss or mutation of the normal second *TP53* allele, p53 tumor suppressor function is lost, and affected individuals have increased risk of bone and soft tissue sarcomas, leukemia, breast cancer, and adrenocortical carcinoma. This patient did not have a typical LFS-associated malignant tumor, and the lack of family history of LFS-associated cancers makes this diagnosis much less likely.

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