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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MUTYH-associated polyposis is an autosomal recessive hereditary colon cancer syndrome characterized by biallelic mutations of the *MUTYH* gene, the development of multiple colonic adenomas, and a predisposition to colorectal cancer. Testing for *MUTYH* mutations should be performed if patients have a history of more than 10 adenomas, meet criteria for serrated polyposis syndrome, or have a known deleterious biallelic mutation of *MUTYH* in their family.[4,5]

Peutz-Jeghers syndrome has an autosomal dominant inheritance pattern and presents with intestinal polyposis and characteristic mucocutaneous melanin deposition. Familial juvenile polyposis also has an autosomal dominant inheritance pattern and is associated with multiple intestinal hamartomatous or juvenile polyps throughout the gastrointestinal tract.

This patient had more than 10 adenomas and therefore met criteria for genetic testing for *MUTYH*. The presence of biallelic *MUTYH* mutations (Y165C) confirmed the diagnosis of *MUTYH*-associated polyposis. The patient also underwent testing for familial adenomatous polyposis (FAP), an autosomal dominant hereditary colon cancer syndrome associated with polyposis that is caused by germline mutations in the tumor suppressor adenomatous polyposis coli (*APC*) gene. Genetic testing for FAP should be considered if a patient has more than 10 adenomas, a personal history of desmoid tumor, or a family history of deleterious *APC* mutations. No *APC* mutations were identified.

4. For surveillance of patients with *MUTYH*-associated polyposis and colon cancer, which *one* of the following is recommended?

a. Upper gastrointestinal series (eg, barium swallow) every 1 to 2 years
b. Annual abdominal ultrasonography
c. No further surveillance is necessary
d. Annual fecal occult blood testing
e. Rectal endoscopy every 6 to 12 months if the patient underwent colectomy with ileal rectosigmoid anastomosis (IRA)

Surveillance is indicated for patients with *MUTYH*-associated polyposis and colon cancer to identify early recurrences and new primary malignant neoplasms. An upper gastrointestinal series every 1 to 2 years or annual abdominal ultrasonography are not recommended modes of screening because the tests are unlikely to be sensitive enough to identify early malignant neoplasms. No further surveillance is inappropriate for these patients because of the high risk of recurrence. Fecal occult blood testing is not a recommended screening tool for patients with a history of colorectal cancer. If a patient has a diagnosis of *MUTYH*-associated polyposis complicated by colon cancer and undergoes colectomy with IRA, an endoscopic evaluation of the rectum should be performed every 6 to 12 months.[4] Esophagogastroduodenoscopy is suggested at baseline and for surveillance at intervals similar to that recommended for FAP.

Our patient continued to have biannual upper and lower gastrointestinal endoscopies and surveillance computed tomography (CT). Two years after completing colon cancer treatment, regularly scheduled surveillance CT revealed an incidental 2.9-cm mesenteric soft tissue mass. The mass was hypermetabolic on positron emission tomography—CT. The patient underwent exploratory laparoscopy with resection of the mass from the small-bowel mesentery and retroperitoneum, along with small-bowel resection. Pathology revealed a desmoid tumor, with immunostains negative for CD117, S-100, desmin, smooth muscle actin, anaplastic lymphoma kinase, human melanoma black, and epithelial membrane antigen and nuclear positivity for β-catenin, consistent with desmoid tumor. Sulindac therapy was initiated postoperatively.

5. Which *one* of the following is a common feature of desmoid tumors?

a. Local recurrence
b. Association with systemic symptoms (eg, fever, weight loss)
c. Liver metastasis
d. Bone metastasis
e. Association with LS

Desmoid tumors are also known as *aggressive fibromatoses*, described as a benign proliferation of fibrous tissue, that commonly recur locally after resection and may invade and compress nearby structures.[6] Association with systemic symptoms (eg, fever, weight loss) has not been described. Although the tumors may have aggressive local activity, they cannot

metastasize. Lynch syndrome is commonly associated with ovarian and endometrial malignant neoplasms, and FAP is associated with fibromas and desmoid tumors. Desmoid tumors are not associated with LS. The extracolonic manifestations of *MUTYH*-associated polyposis are not well described, but the occurrence of desmoid tumor has been reported.[7]

Six months postoperatively, the patient had an additional screening CT of the abdomen and pelvis that revealed a left pelvic mass (2.9 cm). With a presumptive diagnosis based on imaging characteristics of recurrent desmoid tumor, observation was chosen as the best initial strategy. However, after observation for 8 weeks, repeated CT revealed enlargement of the mass (3.4 cm). Therefore, to clarify the diagnosis, the patient underwent laparoscopic exploration with incomplete resection of the mass and peritoneal biopsies. Pathologic examination revealed endometrial adenocarcinoma. She subsequently underwent complete excision of the mass; no involved lymph nodes were identified on left pelvic lymphadenectomy. She was referred for adjuvant carboplatin-paclitaxel chemotherapy for a planned 6 cycles.

DISCUSSION

Lynch syndrome and FAP are the most prevalent hereditary colon cancer syndromes. Lynch syndrome is characterized by autosomal dominant inheritance of a germline mutation in an MMR gene, most commonly *MLH1*, *MSH2*, *MSH6*, and *PMS2*. The most common extracolonic manifestations of LS are endometrial and ovarian cancer.[8] Familial adenomatous polyposis also is an autosomal dominant syndrome that is caused by mutations in the *APC* gene and characterized by the presence of hundreds of colonic polyps and development of colorectal cancer in nearly all affected patients. The attenuated form of FAP manifests similarly to classic FAP but with fewer polyps and a later age at onset of colorectal cancer. Extracolonic manifestations of FAP include duodenal cancer, gastric polyps, osteomas, congenital hypertrophy of the retinal pigment epithelium, epidermoid cysts, fibromas, dental abnormalities, and desmoid tumors.[8]

A more recently identified hereditary colorectal cancer syndrome is *MUTYH*-associated polyposis, first described in 2002.[7] *MUTYH*-associated polyposis is phenotypically similar to the attenuated form of FAP, typically with 15 to 100 colonic adenomas and an older age at presentation (45-56 years). The most common extracolonic manifestation of the syndrome is duodenal adenoma; less common manifestations are congenital hypertrophy of the retinal pigment epithelium, hyperplasia of fundic glands, pilomatricoma, and osteoma. One case report described a desmoid tumor in association with the syndrome.[7]

In our patient with no family history of colon cancer, stage IIA colorectal cancer was diagnosed and treated with colectomy, IRA, and adjuvant chemotherapy. She later underwent genetic testing, and *MUTYH*-associated polyposis was diagnosed. Surveillance for patients with *MUTYH*-associated polyposis and a history of colon cancer who have undergone colectomy with IRA should include endoscopic evaluation of the rectum every 6 to 12 months, baseline esophagogastroduodenoscopy, and an annual physical examination.[4] Because this patient had multiple duodenal and gastric polyps at the time of diagnosis, she continued to have biannual esophagogastroduodenoscopy. Routine screening with abdominopelvic CT is not specifically recommended for *MUTYH*-associated polyposis, but current national guidelines support annual CT evaluation of the chest, abdomen, and pelvis for patients with stage II colon cancer and a high risk of recurrence. This patient elected to undergo surveillance CT, and an intra-abdominal desmoid tumor was diagnosed incidentally 2 years after her initial diagnosis of colon cancer and confirmation of a genetic syndrome.

Desmoid tumors are locally aggressive and infiltrative tumors with a high rate of local recurrence and no metastatic potential. They occur in 10% to 20% of patients with FAP.[8] Treatment options include observation, surgical resection for well-circumscribed tumors, and radiation alone or in combination with surgical or systemic therapy. Systemic therapies include nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, sulindac), antihormonal therapies (eg, tamoxifen, toremifene), tyrosine kinase inhibitors (eg, imatinib, sorafenib), and cytotoxic chemotherapy (eg, anthracyclines, methotrexate, vinca alkaloids).[6] Recent evidence suggests that systemic therapies for desmoid tumors are used more frequently than surgical approaches.[9] Although limited data support the use of systemic therapy, including

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NSAID therapy in the adjuvant setting, given the favorable adverse effect profile and potential reduction in recurrence risk, long-term NSAID therapy after surgical treatment may be offered to selected patients. The WNT/β-catenin signaling pathway is critical to the pathogenesis of desmoid tumors.[10] Results of trials evaluating WNT pathway inhibitors[11] are awaited eagerly because they may offer a novel therapeutic approach for patients with unresectable desmoid tumors. As previously mentioned, only one published case report to date has described a desmoid tumor in the setting of *MUTYH*-associated polyposis.

Endometrial adenocarcinoma is a relatively common extracolonic manifestation of LS. This feature has been described previously in association with *MUTYH*-associated polyposis in 4 patients, one of whom had the appearance of desmoid tumor on imaging but endometrial cancer confirmed later, similar to our case.[12]

These findings highlight the diverse presentation of *MUTYH*-associated polyposis syndrome and underscore its similarity to FAP and LS. Further research into the epidemiology and natural history of *MUTYH*-associated polyposis is required to determine whether routine abdominopelvic CT screening for extraintestinal manifestations (eg, desmoid tumors) or screening for endometrial cancer should be offered to all carriers of this syndrome.

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CORRECT ANSWERS: 1. b. 2. d. 3. c. 4. e. 5. a