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Case 19-2010: A 35-Year-Old Man with Adenocarcinoma of the Cecum

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Presentation of Case

A 35-year-old man was seen in the outpatient cancer center of this hospital because of adenocarcinoma of the cecum.

The patient had been well until approximately 3 weeks before this evaluation, when he passed bright red stools on several days and discomfort developed in the left side of the abdomen, most noticeably after eating. Eighteen days before this evaluation, he saw his primary care provider. Computed tomographic (CT) scans of the abdomen, obtained at another hospital that day, showed thickening of the wall of the cecum and appendix, as well as multiple small nodules in the greater omentum. The next day, an upper gastrointestinal radiographic series showed a large, lobular mass near the ileocecal valve, extending into the cecum, and an extrinsic mass surrounding the terminal ileum. Three days later, colonoscopic examination revealed an edematous and erythematous ileocecal valve, with a friable, hemorrhagic ulcer. Pathological examination of biopsy specimens of the ulcer showed invasive adenocarcinoma that ranged from well differentiated to moderately differentiated.

One week before the current evaluation, combined CT and positron-emission tomographic (PET) scans, obtained after the injection of 20.3 mCi of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG), showed a focus of intense tracer uptake in the cecal region, multiple small omental soft-tissue nodules that did not show ¹⁸F-FDG avidity, a small volume of ascites in the pelvis, and several small pulmonary nodules (9 mm in diameter) that showed low-level tracer uptake. The patient was referred to the cancer center of this hospital.

The patient's bowel habits were unchanged, and he had had no bleeding since the earlier episode. He had hyperlipidemia, and he had undergone bilateral herniorrhaphies as a child;

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he had also received a periodontal graft and had undergone wisdom-teeth extractions in the past. He had lost approximately 4.5 kg of body weight during the previous month, which he attributed to increased exercise and a change in his diet, and generally felt well. His only medication was atorvastatin, and he had no known allergies. He was married with children and worked in an office position. He exercised regularly, drank alcohol socially, and did not smoke or use illicit drugs. His father had hyperlipidemia, his mother was healthy, one sibling had died in an accident, the other sibling was healthy, one grandmother had died of a myocardial infarction, and one grandfather had had coronary-artery bypass surgery when he was in his 50s. There was no family history of colon polyps or cancer.

On examination, the patient appeared well and the vital signs were normal. The height was 188.0 cm, the weight 88.9 kg, and the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) 25.2. The abdomen was soft, with no tenderness, distention, hepatomegaly, splenomegaly, lymphadenopathy, or palpable masses. The remainder of the examination was also normal. The serum level of carcinoembryonic antigen was 10.2 ng per milliliter (reference range, 0.0 to 2.5). Other laboratory-test results were normal, including the hematocrit; measurements of hemoglobin, white cells, electrolytes, glucose, total protein, globulin, albumin, and calcium; and tests of coagulation and renal and hepatic function. Pathological examination of the biopsy specimens at this hospital showed moderately differentiated, invasive adenocarcinoma; immunostaining for MLH1, MSH2, MSH6, and PMS2 revealed intact nuclear staining in tumor cells.

A management decision was made.

Differential Diagnosis

Dr. David P. Ryan: May we review the radiologic images?

Dr. Dushyant V. Sahani: A whole-body PET-CT scan obtained without the administration of intravenous or oral contrast material (Fig. 1) shows a suspicious masslike thickening in the region of the cecum on the CT image (Panel A), associated with intense ^{18}F -FDG uptake (Panel B). Numerous soft-tissue nodules were scattered throughout the abdomen and pelvis (Panel C), and there were nodules in the lungs (Panel D). The peritoneal nodules did not show ^{18}F -FDG activity, but the lung nodules did show low-level ^{18}F -FDG uptake. These findings are compatible with metastatic disease in the lung, possibly from a malignant neoplasm in the cecum. The nodularity in the abdomen and pelvis that was seen on the CT images is suggestive of peritoneal carcinomatosis.

PET scanning is usually not very sensitive in the detection of peritoneal metastases. Small tumor nodules (<2 cm in diameter) and mucinous cancers are characterized by low or no ^{18}F -FDG uptake and therefore can be missed on a PET examination.

Dr. Ryan: This 35-year-old man presents with a mass in the cecum that has been shown to be adenocarcinoma, with radiologic evidence of metastases to the peritoneum and lung. This case raises several interesting questions. Is this a primary colon cancer, or could the tumor have arisen in another site? Why did he get this cancer at such a young age? Assuming it is a primary colon cancer, is there a role for surgery, meaning primary resection and cytoreduction of peritoneal carcinomatosis? Finally, what is the role for chemotherapy, and are we likely to cure this patient?

Although this is most likely a primary colon cancer, other cancers that could mimic this presentation include a small-bowel cancer, appendiceal cancer, and a metastatic carcinoma from another site, particularly from the upper gastrointestinal tract, pancreas, or bile duct. There are two major types of epithelial cancers of the appendix: peritoneal adenomucinosis

with benign-appearing cells that produce pseudomyxoma peritonei, and adenocarcinoma. These appendiceal tumors can exist anywhere along the spectrum from benign-appearing adenomucinosis to very aggressive adenocarcinoma.¹ This patient's presentation and the findings on imaging are not consistent with pseudomyxoma peritonei, and the presence of an ulcerated lesion in the cecum makes a primary adenocarcinoma of the appendix unlikely.

Colorectal Cancers in Young Patients

As many as 15% of colorectal adenocarcinomas occur in patients younger than 50 years of age — the age when we routinely start screening for such cancers. Only 0.1% of all colon cancers occur in patients before 20 years of age, and 1% occur between 20 and 34 years of age. The annual incidence rises from 10 cases per 1 million at the age of 20 years to 100 cases per 1 million at the age of 45 years.² Nonetheless, colon cancer represents the third leading cause of cancer-related death in the United States for men between 20 and 39 years of age and the fourth leading cause of cancer-related death for women in this age group.² Although younger patients tend to present with advanced-stage disease more commonly than older patients do, it is not clear whether, stage for stage, the prognosis differs from that for older patients.³

In a young patient with colon cancer, hereditary forms need to be considered, including familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer (HNPCC), and MutY homologue (*MYH*)–associated polyposis. All these syndromes are associated with early-onset colon cancer, but HNPCC-associated colon cancers are noteworthy for occurring in the right colon more often than in the left colon, as in this patient. Other factors that may confer a predisposition to colorectal cancer in the young include inflammatory bowel disease and a history of abdominal or pelvic irradiation, which do not pertain to this patient. The incidence of colorectal cancer in the young is believed to be increasing,³ for reasons that are not known; increased rates of obesity have been suggested, since increased BMI and abdominal girth and decreased physical exercise have been reported to be associated with an increased risk of colon polyps, a precursor to cancer.⁴ This patient was not obese and did not have a history of polyps.

Hereditary cancer syndromes and other predisposing factors appear to account for less than 20% of colon cancers in persons under the age of 40 years.³ This patient had no family history of cancer, and he did not have colon polyps; thus, it is unlikely that the cancer resulted from an inherited predisposition to colon cancer.

May we review the colonoscopic-biopsy specimen?

Pathological Discussion

Dr. Mikhail Lisovsky: The colonoscopic-biopsy specimen revealed moderately differentiated adenocarcinoma of the cecum. This was characterized by branching glands infiltrating the desmoplastic stroma, cytologic features of mucin depletion, enlargement and hyperchromasia of the nuclei, and increased mitoses (Fig. 2A).

In a patient younger than 50 years of age, familial colorectal cancer, such as HNPCC, also known as the Lynch syndrome, is a strong diagnostic consideration. Microsatellite-instability analysis was performed on the colonoscopic-biopsy specimen with the use of a standardized polymerase-chain-reaction (PCR)–based approach and primers to 10 different microsatellite DNA loci. Changes in the lengths of the microsatellites were determined by sizing the PCR products with the use of capillary electrophoresis. No microsatellite instability was detected. Moreover, loss of heterozygosity of p53 and adenomatous polyposis coli (APC) genes was detected, indicating chromosomal instability, which is a

feature of the classic APC- β -catenin pathway of colorectal carcinogenesis. Immunohistochemical analysis of the products of DNA mismatch-repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* revealed intact nuclear staining in tumor cells. These results argue against the diagnosis of HNPCC (the Lynch syndrome).

Discussion of Management

Dr. Ryan: According to the American Joint Commission on Cancer (AJCC) staging system for colon cancer, which takes into account the depth of tumor invasion, the number of lymph nodes containing metastatic cancer, and the presence or absence of distant metastases, this patient has stage IV colon cancer, with distant metastases (peritoneal carcinomatosis and lung involvement).⁵ Because of the advanced stage of the cancer, a multidisciplinary approach is required to determine the relative roles and timing of surgery, chemotherapy, and possibly radiation therapy. Dr. Ferrone, would you discuss the role of surgery for this patient?

Surgical Management of Advanced Colon Cancer and Peritoneal Carcinomatosis

Dr. Cristina R. Ferrone: Often, when a patient presents with colon cancer, we think of surgical resection as the first line of treatment. However, in a patient with metastatic disease, a multidisciplinary evaluation is required to determine the roles of medical oncologists, surgeons, and radiation oncologists in the removal of the primary tumor, especially if it is asymptomatic.

Initial surgical resection has advantages and disadvantages. Laparotomy with resection of the primary tumor permits a thorough evaluation of the stage of the primary tumor and the extent of intraabdominal disease, since peritoneal carcinomatosis and very small metastases often cannot be visualized on imaging. Surgical resection also provides control of the primary tumor, thereby reducing the risk of bleeding, obstruction, or perforation during subsequent treatments. A recent meta-analysis of 850 asymptomatic patients with stage IV colorectal cancer showed that among patients treated primarily with chemotherapy, intestinal obstruction developed in 14% of patients, and hemorrhage occurred in 3% of patients.⁶

The major disadvantage of an up-front operation is the delay of chemotherapy, especially in cases in which a surgical complication (e.g., an anastomotic leak or wound infection) occurs. A postoperative bowel obstruction caused by adhesions can also delay or interrupt chemotherapy. Of the patients in the meta-analysis who underwent surgical resection first, 12% had major complications, including obstruction, hemorrhage, sepsis, and an anastomotic dehiscence.⁶

Resection of the primary tumor is not associated with an overall survival advantage, and most patients never have a complication from the primary tumor. Therefore, we often advise proceeding straight to chemotherapy.⁷

Another debated topic is the role of surgical debulking and intraperitoneal chemotherapy in patients with peritoneal cancers. A review of small clinical trials and surgical series by a consensus conference of the Society of Surgical Oncology⁸ concluded that in patients with peritoneal carcinomatosis who do not have evidence of metastasis outside the abdomen, cytoreductive surgery in combination with intraperitoneal chemotherapy and postoperative systemic chemotherapy may result in a median survival of up to 42 months, if complete cytoreduction (removal of all tumor deposits >2.5 mm in diameter) is achieved before chemotherapy. It is not clear whether this type of approach is as effective in the most common form of carcinomatosis — colon cancer — as in rare tumors such as the

appendiceal cancers. At this hospital, this approach in patients with metastatic colon cancer is considered investigational, to be performed only in the context of a clinical trial.

Chemotherapy for Peritoneal Carcinomatosis from Colon Cancer

Dr. Ryan: What is the prognosis for this patient with peritoneal carcinomatosis, and is there chemotherapy that will be effective in improving his survival? The AJCC staging system for colon cancer predicts 5-year survival for only 5 to 7% of patients with stage IV disease.⁵ In the Köhne model, patients with metastatic colon cancer are stratified according to good (low) risk, intermediate risk, and poor (high) risk on the basis of the following features: performance status, number of disease sites, alkaline phosphatase level, and whitecell count.⁹ Before the availability of multiagent chemotherapy, the median survival was 15 months among patients with a good risk, 10.7 months among patients with an intermediate risk, and 6.4 months among patients with a poor risk, such as this one.⁹ The presence of peritoneal carcinomatosis, which this patient has, was associated with a median survival of 7.7 months, as compared with 11.6 months if peritoneal carcinomatosis was not present.

Is there effective chemotherapy that will prolong the life of this patient? Before the late 1990s, fluorouracil was the only active chemotherapy for metastatic colon cancer, and only about 1% of patients treated with this drug survived longer than 5 years.¹⁰ Since the late 1990s, the chemotherapy regimens for colon cancer have been expanded to include irinotecan, oxaliplatin, and the biologic agents cetuximab, panitumumab, and bevacizumab.¹¹ A randomized trial comparing regimens of fluorouracil, leucovorin, and irinotecan (FOLFIRI); fluorouracil, leucovorin, and oxaliplatin (FOLFOX); and irinotecan and oxaliplatin showed that the median survival among all patients was approximately 20 months, and approximately 10% were alive at 5 years.¹² There was no difference in efficacy among the various combinations. Thus, any of these combinations would offer some benefit to our patient.

What about the new targeted agents bevacizumab and cetuximab? Bevacizumab is a monoclonal antibody that blocks the action of vascular endothelial growth factor (VEGF) and was approved by the Food and Drug Administration in 2004 for use in patients with metastatic colon cancer. Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor (EGFR) and was approved for use in patients with metastatic colorectal cancer that is refractory to irinotecan. Either of these agents may improve progression-free survival when added to FOLFOX or FOLFIRI.^{11,13,14} Gastrointestinal perforation occurs in about 2% of patients taking bevacizumab for colon cancer; perforation is associated with an intact primary tumor¹³ and peritoneal carcinomatosis,¹⁵ both of which are of concern in this patient. Cetuximab has three major adverse effects — acneiform rash, diarrhea, and allergic reactions — but it is not associated with bowel perforation. For this patient, we would like to consider adding either bevacizumab or cetuximab to a combination chemotherapy regimen.

We wanted to confirm that the patient's primary tumor was in the cecum and to determine the extent of disease in the abdomen. In addition, most of the patient's symptoms at presentation appeared to be due to the primary tumor. For this reason, we recommended resection of the primary tumor, which was performed by Dr. Michael J. Zinner. We planned subsequent chemotherapy with FOLFIRI, with the addition of either bevacizumab or cetuximab at cycle 2.

Dr. Michael J. Zinner (Surgery, Brigham and Women's Hospital, Boston): At laparotomy, we removed a portion of the omentum to confirm by examination of frozen section that the patient had metastatic cancer, which he did. The preoperative imaging had identified precisely where the omental masses were located. There were pelvic metastases, less than 1

cm in diameter, which had not been seen on imaging. We removed the right side of the colon, including the distal portion of the ileum and right transverse colon. A suspicious extraluminal nodule was found close to the area of proposed anastomosis and was a focus of metastatic cancer. We then performed a standard stapled anastomosis.

Further Pathological Discussion

Dr. Lisovsky: The right- colectomy specimen had an ulcerated cecal mass, 5.0 cm in diameter, extending into the wall of the terminal ileum. Histologically, glands of moderately differentiated adenocarcinoma invaded through the wall of the cecum (Fig. 2B) and were present on the surface of the serosa (Fig. 2C). Perineural invasion and a mild-to-moderate peritumoral lymphoid response were noted. The closest radial margin was less than 0.1 cm from the tumor. Metastatic adenocarcinoma involved 2 of 32 regional lymph nodes (Fig. 2E). Nodules of metastatic adenocarcinoma were also present in the greater omentum (Fig. 2D), pelvic peritoneum, and serosa of the transverse colon. According to the AJCC tumor-node-metastasis (TNM) staging system, the staging was T4N1M1.

Further Discussion of Management

Dr. Jeffrey A. Engelman: Consideration was given to the use of cetuximab in this patient. Cetuximab is similar to many of the targeted therapies that are used in solid tumors, in that it is directed against a receptor tyrosine kinase (RTK). Cancer cells with constitutively activated RTKs depend on the active receptor for growth and survival. Thus, when the RTK is inhibited, the cancer cell stops growing and undergoes apoptosis. In colorectal cancer, the absence of *KRAS* mutations and the presence of EGFR ligands predict sensitivity to cetuximab.¹⁶ Activating *KRAS* mutations are observed in 30 to 40% of colorectal adenocarcinomas (www.sanger.ac.uk/genetics/CGP/cosmic/), as well as almost all pancreatic cancers and many lung cancers. EGFR and other RTKs act through downstream pathways, two of which seem to be central to the “RTK-addicted” cancers: the PI3K–AKT and the Raf–MEK–ERK pathways^{17–19} (Fig. 3). The Raf–MEK–ERK pathway is activated by *KRAS*, and when *KRAS* is mutated, it constitutively activates this pathway, most likely rendering it independent of EGFR. In such cells, MEK–ERK signaling will not be downregulated by inhibiting EGFR. Clinical trials have shown that the presence of *KRAS* mutations leads to a markedly diminished responsiveness to cetuximab.^{14,20,21} For this reason, testing of tumor tissue for the presence of *KRAS* mutations is recommended before initiating therapy with cetuximab.²²

Dr. Lisovsky: To evaluate the mutation status of *KRAS*, genomic DNA was extracted from the paraffin-embedded tumor tissue, and *KRAS* sequence analysis of exon 2 was performed with the use of PCR capillary electrophoresis, in the laboratory of Dr. A. John Iafrate. No mutations were identified.

Dr. Ferrone: One month after surgery, the patient was started on FOLFIRI. Three days after the first cycle of chemotherapy, the patient was admitted to the hospital with a small-bowel obstruction, which required reexploration, lysis of adhesions, and resection of a segment of small bowel.

Dr. Ryan: After spending approximately 2 weeks in the hospital with bowel obstruction, the patient was terrified of having another gastrointestinal event; thus, we wanted to avoid bevacizumab. Since his tumor was *KRAS* wild-type, we decided to add cetuximab instead of bevacizumab to his regimen. He was treated for 6 months with FOLFIRI and cetuximab and had an excellent response. At the end of 6 months, CT scans showed no obvious evidence of metastatic disease, and the patient began a chemotherapy holiday. Unfortunately, approximately 6 months later, his level of carcinoembryonic antigen began to rise, and the

lung nodules enlarged. We reinitiated treatment with FOLFIRI and cetuximab, and his disease remained stable for another 6 months. At that time, new bone lesions were seen on scans, and the level of carcinoembryonic antigen rose again. His chemotherapy regimen was switched to FOLFOX and bevacizumab. After 3 months, the bone lesions had progressed and pain developed, and palliative irradiation and pain medication were required. We discussed several phase 1 clinical trials, but the patient ultimately declined. Recently, just over 2 years since his initial diagnosis, he opted to pursue palliative care only, in order to spend the most possible time with his family before he dies.

Anatomical Diagnosis

Adenocarcinoma of the cecum with metastases to regional lymph nodes and peritoneum (AJCC stage T4N1M1).

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Figure 1. Selected Images from a Whole-Body Combination CT and Positron-Emission Tomographic Examination

An axial CT scan of the abdomen (Panel A) shows a masslike thickening in the cecum (circle) with corresponding intense uptake of ^{18}F -fluorodeoxyglucose (Panel B). There are numerous nodules in the peritoneum (Panel C, arrow) and the lungs (Panel D, arrow), which are consistent with metastatic disease.

Figure 2. Biopsy and Resection Specimens Revealing Adenocarcinoma of the Cecum (Hematoxylin and Eosin)

A colonoscopic-biopsy specimen (Panel A) shows invasive, moderately differentiated adenocarcinoma. The resection specimen (Panel B) reveals deeply invasive adenocarcinoma. Adenocarcinoma is present on the visceral serosa (Panel C) and in the omentum (Panel D), as well as in a regional lymph node (Panel E).

Figure 3. Signaling Pathways That Regulate Responses to EGFR Inhibitors

In a subgroup of cancers harboring wild-type *KRAS* (left), a specific receptor tyrosine kinase (RTK) (e.g., epidermal growth factor receptor [EGFR]) controls the PI3K–AKT and MEK–ERK signaling pathways, which are down-regulated by RTK inhibition.^{18,19} Cancers with mutant *KRAS* (right) have constitutive activation of the MEK–ERK pathway (and possibly the PI3K–AKT pathway). Therefore, these signaling pathways are not down-regulated in response to RTK inhibitors. Arrows indicate activation, dead-end lines () inhibition, and dashed lines uncertainty about the signaling connection. BAD denotes B-cell lymphoma 2 (BCL2)–associated agonist of cell death, BIM BCL2-interacting mediator of cell death, ERK extracellular-signal–regulated kinase, GDP guanosine diphosphate, GTP guanosine triphosphate, Mcl-1 myeloid-cell leukemia sequence 1, MEK mitogen-activated protein–extracellular-signal–regulated kinase, mTOR mammalian target of rapamycin, P phosphorylation, PDK phosphoinositide-dependent protein kinase 1, PIP2 phosphatidylinositol 4,5-bisphosphonate, PIP3 phosphatidylinositol 3,4,5-triphosphate, PI3K phosphatidylinositol 3-kinase, PRAS40 AKT1 substrate 1, and RSK ribosomal protein S6 kinase. Asterisks indicate activating mutations.