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Mismatch repair gone awry: Management of Lynch syndrome

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Abstract

The hallmark of Lynch syndrome involves germline mutations of genes important in DNA mismatch repair. Affected family kindreds will have multiple associated malignancies, the most common of which is colorectal adenocarcinoma. Recently, evidence has shown that clinical diagnostic criteria provided by the Amsterdam Criteria and the Bethesda Guidelines must be linked with microsatellite instability testing to correctly diagnose Lynch syndrome. We present a case of metachronous colorectal adenocarcinomas in a patient less than 50 years of age, followed by a discussion of Lynch syndrome, with an emphasis on surveillance and prevention of malignancies.

Keywords: Lynch syndrome; Mismatch repair; Microsatellite instability; Colorectal cancer; Hereditary gastrointestinal malignancies

1. Introduction

A 47-year-old Caucasian man, self employed mason and former marine with otherwise no significant past medical history, initially presented in October 2002, when he developed acute right lower quadrant abdominal pain. He had

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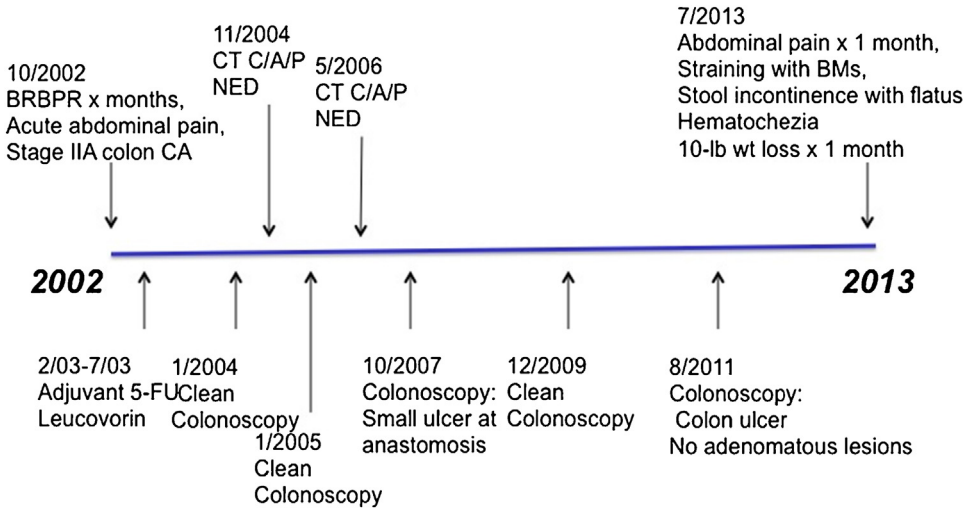

Fig. 1. Timeline in case presentation.

bright red blood per rectum (BRBPR) for months initially attributed to hemorrhoids. He was taken to the operating room for an exploratory laparotomy and appendectomy, but intraoperative findings of a right-sided colon mass changed the procedure to a right hemicolectomy. He was surgically staged as Stage IIA (pT3N0, with no metastatic disease on subsequent computed tomography (CT) imaging). His tumor showed a microsatellite instability (MSI)-high phenotype, with MSI in 9 of 10 markers tested. The immunohistochemistry (IHC) report at the time further detected a "deficiency of PMS2 and/or MSH6, with normal expression of MSH2 and MLH1." He received a course of adjuvant chemotherapy with 5-fluorouracil, which was complete in July 2003.

His family history was significant for various malignancies. His mother had developed colon cancer in her 30s, with recurrences and eventually had a total colectomy. She subsequently also had breast cancer at age 68. His paternal grandfather also had colon cancer in his 70s. One of his three sisters developed colon cancer aged mid-40s, and another sister developed a possible brain tumor. He had 3 brothers, one of whom had died of liver cancer.

In the intervening years, he underwent routine surveillance follow up with no evidence of disease on annual CT scans until 2006, and subsequently had clean colonoscopies every 2 years, including one in August 2011 (Fig. 1).

In July 2013, he again presented with abdominal pain for 1 month, straining with bowel movements, stool incontinence with flatus, and hematochezia.

On exam, he had a tender abdomen in the left lower quadrant, without rebound or guarding. His rectal exam demonstrated a firm mass palpable with tenderness to palpation and gross blood on inspection. Labs were significant for a normal CEA of 0.7, anemia with hemoglobin 10.7 g/dL, with MCV 82, normal WBC count of 5.5 mL^{-1}, and normal platelet count of 291,000 mL^{-1}. He underwent a CT of the abdomen and pelvis that showed new irregular circumferential soft tissue around the rectum with surrounding lymphadenopathy, with no clear fat plane between rectum and prostate. Positron-emission tomography (PET) scanning showed the same findings, with FDG avidity in the wall thickening, as well as multiple FDG-avid retroperitoneal and pelvic lymph nodes.

He subsequently underwent colonoscopy, demonstrating a rectal mass 15 cm from the anal verge, occupying 50–74% of the circumference. The tumor was friable and bled on contact. Biopsy of this lesion showed high grade, poorly differentiated adenocarcinoma (Fig. 2).

2. Discussion

2.1. Background of Lynch syndrome

Up to 30% of colorectal cancers (CRC) are inherited, and known syndromes account for only 2-5% of all cases (Table 1). The two most common syndromes are Lynch syndrome and familial adenomatous polyposis (FAP), with

Table 1
Mutations affected in hereditary colorectal cancer syndromes.

Cancer Syndrome	Mutation
Lynch syndrome	MLH1, MLH2, MSH6, PMS2, EpCAM
Familial adenomatous polyposis	APC
Mixed polyposis syndrome	GREM1
Ashkenazi colorectal polyposis	APC I1307K
Hereditary breast & colorectal cancer	CHEK2
MUTYH-associated polyposis	MUTYH
Syndromes with hamartomatous lesions	Mutation
Peutz-Jeghers	STK11
Familial Juvenile polyposis	SMAD44, BMPR1A
Cowden disease	PTEN
Bannayan–Ruvalcaba–Riley	PTEN