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SHORT REPORT

Inflammatory bowel disease and familial adenomatous polyposis☆

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Abstract

Background: Inflammatory bowel disease (IBD) and familial adenomatous polyposis (FAP) are uncommon diseases and both are associated with marked increased risk of colorectal cancer.
Methods: We present a patient diagnosed in parallel with ulcerative colitis and FAP. Mutational analysis of the APC germline and somatic DNA was performed by sequencing.
Results: This patient's phenotype consisted of polyps only on the right side of the colon (cecum and ascending colon) whereas the area affected by ulcerative colitis (descending colon and rectum) was free of polyps on endoscopy and microscopic adenomas on histology. This raises the possibility that mosaicism or inflammation in the presence of active ulcerative colitis modified the phenotypic expression of adenomatous polyposis in the left colon. Mosaicism was excluded by DNA analysis.
Discussion: This case of a patient diagnosed with both inflammatory bowel disease and familial adenomatous polyposis offers potential insights into the distinct pathogenesis of cancer susceptibility within these syndromes, and suggests that a collision of phenotypes may influence their mutual presentation. Both of these conditions independently increase the risk of colorectal cancer.

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1. Introduction

Ulcerative colitis (UC) is a relapsing inflammatory bowel disease, associated with an increased risk of colorectal cancer of approximately two to five fold over general population.[1] This increased risk of cancer is associated with disease severity, extent and duration.[2]

About 5 to 10% of colorectal cancer is due to an identifiable genetic cause. Familial adenomatous polyposis (FAP) is a genetic condition which predisposes individuals to 100 s to 1000 s of colorectal polyps, with an average age of onset at 16 years. FAP is caused by mutations in the *APC* gene and is inherited in an autosomal dominant fashion.[3] Without appropriate intervention, risk of colorectal cancer in individuals with FAP is virtually 100%.[3,4]

2. Case presentation

A 59 year old male was referred to the outpatient gastroenterology clinic for assessment of diarrhea for 5 months. He described having greater than five watery bowel movements per day associated with urgency and occasional rectal bleeding. This was a change from previous bowel frequency of one well formed stool per day. There was no history of infectious risk factors such as travel or sick contacts. He did not report any previous history of rectal bleeding, chronic diarrhea, extra-intestinal features such as arthritis, erythema nodosum or oral aphthous ulceration.

His only medications were ranitidine and ibuprofen as needed (less than one dose per week). His only medical history was that of gastro-esophageal reflux, dyslipidemia and benign positional vertigo. He did not have a personal or family history of inflammatory bowel disease or microscopic colitis. However, the family history was significant for his father having died from metastatic colorectal cancer at age 77 and his sister having a clinical diagnosis of familial polyposis at age 50 without confirmatory genetic testing, treated with colectomy (Fig. 1a).

His bloodwork was normal, including erythrocyte sedimentation rate, C-reactive protein, celiac serology and infectious stool studies.

Upper endoscopy with random biopsies of the duodenum revealed multiple sessile polyps in the fundus along with a single flat polyp located at the ampulla. Biopsies of the stomach revealed fundic gland polyps, two of which had histologic evidence of low grade dysplasia. One gastric polyp was an adenoma (Fig. 1b), as was the ampullary polyp. Colonoscopy showed many sessile 2–10 mm polyps in cecum, ascending colon and transverse colon that were too numerous to resect completely (Fig. 1c). Also, a diffuse area of granular, erythematous mucosa with loss of vascularity was noted extending from anus to descending colon (40 cm from anal verge) (Fig. 1d). Biopsies of cecal polyps were consistent with adenomas (Fig. 1e). Biopsies from the descending colon and rectum showed active ulcerative colitis without dysplasia (Fig. 1f). Though his laboratory parameters were normal (including ESR and CRP) his acute onset symptoms of diarrhea and hematochezia and endoscopic findings of left sided colitis were consistent with a flare of ulcerative colitis.

His constellation of findings was consistent with a clinical diagnosis of FAP and he was referred to Cancer Genetics. DNA sequence analysis of *APC* was performed on a blood sample in a CLIA-certified lab. Independent verification of the identified mutation was performed in our research lab from a second tube of blood. Adenomas from right colon and areas of ulcerative colitis from left colon were obtained at the time of surgical resection through the University of Michigan Tissue Core. Frozen sections of affected areas were evaluated by routine hematoxylin and eosin (H&E) stains by a surgical pathologist. Areas of at least 70% cellularity within the adenomas and areas of ulcerative colitis, as well as adjacent normal tissue were microdissected, and DNA was extracted using a TRIzol Reagent (Life Technologies, Gaithersburg, MD). PCR and capillary sequencing confirmed a deletion in exon 4, of adenosine and thymidine residues at position 426_427of *APC* in the genomic DNA. The mutation was also identified in DNA from samples of adenoma, ulcerative colitis and adjacent normal tissue (Fig. 2). This mutation is predicted to result in a premature protein truncation and confirms a molecular genetic diagnosis of FAP.

Bilateral or multiple congenital hypertrophy of the retinal pigment epithelium (CHRPE) is another finding seen in association with FAP, this patient did not undergo an indirect ophthalmoscope exam through a dilated pupil since genetic testing confirmed a molecular diagnosis of FAP.

With molecular confirmation of FAP and histologic confirmation of ulcerative colitis the patient was referred to colorectal surgery and underwent total abdominal colectomy with J-pouch creation and ileo-anal anastamosis as a single procedure. This was intended to be a curative treatment for both FAP and ulcerative colitis.

3. Discussion

The risk of intestinal cancer in IBD has been identified in both referral center[5,6] and population-based studies[1,7] and ranges between a 2.5 and 5 fold elevation over the general population. Treatment of UC is divided into medical and surgical management. Medical treatment includes anti-inflammatory medications such as amino-salicylates, immunomodulators such as imuran and prednisone along with anti-TNF biologic agents such as infliximab.[8] There is debate whether these medications can decrease the risk of colorectal cancer.[9] Surgical management of UC includes total abdominal or procto-colectomy, which is believed to be curative.

About 5 to 10% of colorectal cancer diagnosis is due to an identifiable genetic cause. The differential diagnosis for these genetic causes includes Lynch Syndrome (formerly described as HNPCC) which accounts for 2–3%, FAP which accounts for 1% and other rare conditions which account for approximately 1%.[10] This patient's personal and family history of polyps and colon cancer led to a clinical diagnosis of FAP. FAP is caused by mutations in the *APC* gene, located on chromosome 5.[3,4] FAP can present with a "classical" or "attenuated" phenotype. While the "classical" phenotype displays >1000 polyps and frequently presents early in life, the "attenuated" phenotype often has <100 polyps and can present much later in age. Mutations in the *APC* gene that have been described to cause the "attenuated" phenotype are typically located in the 5′ or 3′ regions of the gene.[11,12] The risk of colorectal cancer in classic FAP is virtually 100%. These patients are also at risk of developing duodenal,