SHORT REPORT

Inflammatory bowel disease and familial adenomatous polyposis☆

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Received 5 May 2012; received in revised form 28 June 2012; accepted 29 June 2012

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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Grant support: This work was supported in part by the National Cancer Institute RO1 CA81488 (Dr. Gruber), and the University of Michigan's Cancer Center Support Grant (S P30 CA465920).

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KEYWORDS
Familial adenomatous polyposis (FAP);
Ulcerative colitis;
Inflammatory bowel disease (IBD)

Available online at www.sciencedirect.com

Journal of Crohn's and Colitis (2013) 7, e103–e107
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. This increased risk of cancer is associated with disease severity, extent and duration.  

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. Without appropriate intervention, risk of colorectal cancer in individuals with FAP is virtually 100%. 

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 adenomatous polyposis at age 50 without confirmatory genetic testing, referred to Cancer Genetics. 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 426.427 of 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 anastomosis 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 and population-based studies 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. There is debate whether these medications can decrease the risk of colorectal cancer. 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%. 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.  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. The risk of colorectal cancer in classic FAP is virtually 100%. These patients are also at risk of developing duodenal,
ampullary and rarely gastric tumors. Neklason et al. describe two large American kindreds with the identical FAP mutation to our patient (426_427delAT). They describe a highly variable phenotype in affected individuals with this mutation and estimate a cumulative risk of colorectal cancer by age 80 of 69% with a corresponding standardized incidence ratio of 17.9 (95% CI, 8.4–24.7). Management of FAP includes annual surveillance colonoscopy to remove polyps until the polyp burden makes endoscopic removal not feasible. Colectomy is recommended for extensive polyposis. Since the risk of rectal cancer developing after subtotal colectomy in FAP is high, most experts advise total proctocolectomy with ileal pouch anal anastomosis. If rectal tissue is left intact at time of surgery, then yearly flexible sigmoidoscopy must continue to prevent the appearance of neoplasia in this area. Periampullary and duodenal tumors are surveyed with the use of annual forward and side-viewing esophagastroduodenoscopy (EGD).

The hereditary flat adenoma syndrome (HFAS) is an autosomally dominant inherited condition with multiple colonic adenomas (usually less than 100) with a tendency for proximal location that would be consistent with the presentation in our patient. Given its linkage to the FAP locus on 5q
Figure 2  Chromatogram showing a deletion in exon 4, of adenosine and thymidine residues at position 426_427of APC in reference (ceph) and genomic DNA.

and the phenotypic parallels between HFAS and FAP researchers have concluded that HFAS is a variant of FAP. Though our patients’ presentation would be consistent with HFAS, this would not change the diagnosis of FAP, since a mutation was found in APC (confirming a molecular diagnosis of FAP) and HFAS is likely a variant of FAP, similar to the usage of the term Gardner syndrome to reflect a variant of FAP with extra-intestinal manifestations.15

Though attenuated FAP can present with <100 polyps, adenomas are typically distributed throughout the entire colon. In fact, the majority of patients with FAP begin to develop polyps during their childhood, mostly in the distal colon (rectosigmoid). Also, the polyps seen in the right colon of this patient were not consistent with inflammatory pseudopolyps since they were adenomatous. 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 either mosaicism or inflammation accompanying active ulcerative colitis modified the phenotypic expression of adenomatous polyposis in the left colon.

There have been several reports in the literature of somatic mosaicism in patients with FAP. These patients have a wide spectrum of colonic and extra-colonic phenotype depending on the cellular level of mosaicism.17,18 In this case, we have demonstrated the presence of the APC 426-427delAT mutation in genomic, polyposis-affected right colon and non-polyposis, inflamed left colon, therefore eliminating mosaicism as a cause of the observed phenotype. Expert pathology review confirmed the lack of microscopic adenomas and aberrant crypt foci (ACF) in the left colon. This may suggest that inflammation associated with UC suppresses polyposis at a very early stage leading to the lack of even ACF. All of these findings further strengthen our argument that the UC-inflammation modifies the expression of FAP in this patient. To further investigate whether mucosal inflammation acts to suppress polyposis there are several animal models of UC that could be introduced into the APCmin+ mice to model the patient’s symptoms. However, these animal models are limited, as the chemical colitis induced in the UC models differs histologically and in neoplasia development then human disease.19 Most APCmin+mouse models also have a different colonic phenotype then human FAP, with most of the intestinal tumors occurring in the small bowel.20,21 Other reports of inflammatory bowel disease with colonic inflammation (UC or Crohn’s colitis) in patients with FAP may also shed further light on our hypothesis.

This case of a patient diagnosed with both inflammatory bowel disease (ulcerative colitis) 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 markedly increase the risk of colorectal cancer independently. Treatment of both conditions was accomplished with total colectomy with ileoanal anastomosis. The clinical expression of FAP in this case (right sided polyposis without accompanying left-sided polyposis) suggests the hypothesis that mucosal inflammation secondary to UC may alter the formation or expression of adenomas.

Conflict of interest

Guarantor of the article: Stephen B. Gruber, MD, PhD.

Specific author contributions: All authors approved the final draft submitted. Study concept and design, data collection, analysis, interpretation, article preparation and manuscript review: Stephen B. Gruber; study concept and design, data analysis and interpretation, and article preparation: N. Jewel Samadder; data analysis and manuscript review: Jessica Everett and Michele Gornick; data interpretation and manuscript review: Joel K. Greenson.

Financial support: NCI R01 CA81488, NCI P30 CA465920. Potential competing interests: No authors have conflicts of interest to declare.

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