Case Report

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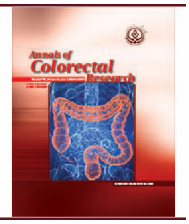

# Colorectal Cancer in People with Cystic Fibrosis under the Age of 40: A Case Series

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## Abstract

**Introduction:** Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene cause cystic fibrosis (CF), a disease that primarily affects the respiratory and gastrointestinal (GI) tracts. The lifetime risk of colorectal cancer (CRC) in patients with CF is approximately 5-10 times that of the general population. In 2018, the CF Foundation CRC Screening Task Force recommended initiating CRC screening in adults with CF at the age of 40 years.
**Case Presentation:** In this case series, we present three cases of females with CF younger than 40 years of age diagnosed with CRC with variable presentations and stages. We discuss the data supporting current CRC screening guidelines in CF in an effort to raise awareness among clinicians regarding young-onset CRC in this population. Furthermore, we aim for this case series to help drive further investigations into the mechanisms underlying CF-related CRC and to open the door to changes in current screening practices.
**Conclusion:** People with CF are at a substantially higher risk of development of CRC relative to the general population. While current CRC screening practices advocate for earlier screening in this population compared to average-risk patients, this case series highlights potential limitations to the current screening guidelines.

**Keywords:** Colon cancer, Colon cancer syndrome, Colonoscopy, Colorectal polyp, Cystic fibrosis, Diagnostic colonoscopy, Hereditary colon cancer, Polyps, Screening colonoscopy, Surveillance colonoscopy

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## Introduction

Cystic Fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, resulting primarily in pulmonary disease but also affecting other organs, including the gastrointestinal (GI) system. The risk of colorectal cancer (CRC) in people with CF is estimated to be 5-10 times greater than that of the general population (1, 2), and prior case reports have demonstrated the potential for earlier-onset CRC in patients with CF (3, 4). In February 2018, the Cystic Fibrosis Foundation (CFF) Colorectal Cancer Screening Task Force recommended that screening colonoscopy in adults with CF start at the age of 40 years (5). Since 2016,

three non-transplanted individuals with CF at the Baylor College of Medicine Adult CF Center (Houston, TX, USA) have been diagnosed with CRC before reaching the age of 40 years. This paper presents their cases, reviews the current literature on CF-associated CRC, and provides insight into whether earlier CRC screening should be considered in patients with CF.

## Case Presentations

### *Case 1*

A 35-year-old female with CF (dF508/3120G-->A; forced expiratory volume in one second (FEV1) 1.6 liters, 51% predicted) presented with anemia and a three-year history of intermittent rectal bleeding without appropriate follow-up care. Her past medical history included endometriosis. Her medications included albuterol sulfate, hypertonic saline, dornase alfa, and pancreatic enzyme replacement therapy (PERT). She was a non-smoker and did not drink alcohol. Her family history included breast, ovarian, and lung cancer. BRCA testing was negative. Colonoscopy revealed a partially obstructing sigmoid adenocarcinoma with appropriate expression of mismatch repair proteins. Staging computerized tomography (CT) showed no evidence of distant metastases, and she underwent robotic-assisted laparoscopic hemicolectomy without any complications. The final pathological stage was T3N2a (stage IIIB). She completed 3 months of adjuvant chemotherapy and currently has no evidence of recurrence.

### *Case 2*

A 35-year-old female with CF (F508/F508 - FEV1 2.18L, 69% predicted) and CF-related diabetes (CFRD) presented with five months of intermittent abdominal pain and, ultimately, overt rectal bleeding. Medications included albuterol sulfate, hypertonic saline, dornase alfa, lumacaftor/ivacaftor, and PERT. Family history was negative for cancer. She was a non-smoker with social alcohol intake. Colonoscopy revealed a large sigmoid adenocarcinoma with appropriate expression of mismatch repair proteins. Staging CT imaging showed a single liver mass, which was biopsied and confirmed to be metastatic (stage IV) CRC. She received combination chemotherapy followed by sigmoidectomy and resection of her liver mass. Soon thereafter, she was found to have biopsy-proven metastatic lung nodules and palliative oral chemotherapy was initiated. Her tumor burden has continued to progress according to interval imaging.

### *Case 3*

A 39-year-old female with a history of CF (F508/1717-1G-->A; FEV1 1.15L, 35% predicted) who was referred to our center for lung transplantation. Her past medical history included systemic lupus erythematosus (SLE). Medications included albuterol sulfate, hypertonic saline, dornase alfa, hydroxychloroquine, and mycophenolate mofetil. She did not smoke or consume alcohol. Colonoscopy was performed as part of pre-transplant screening, and five polyps were resected, ranging from two to six millimeters in size. The six-millimeter descending colon polyp (Figure 1) included a focus of invasive adenocarcinoma; the remaining polyps contained only non-dysplastic tubular adenomas. A left hemicolectomy with curative intent was performed, with a final pathologic stage of T1N0 (Stage I). The patient underwent bilateral lung transplantation four months later.

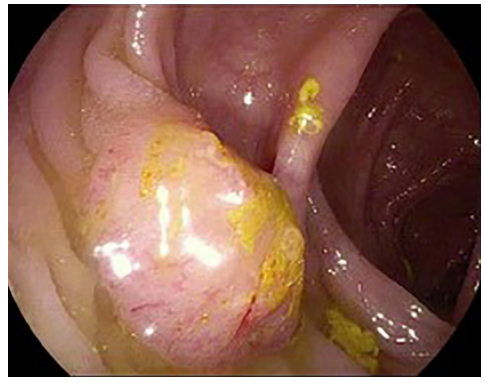

**Figure 1:** Left descending colon polyp which was resected and found to be a moderately differentiated, invasive adenocarcinoma from Case 3.

## Discussion

As of 2019, the median life expectancy of people with CF living in the United States is greater than 46 years (6). Improved survival in CF patients should be celebrated, but living longer also increases the risk for developing cancer (7, 8). Since CRC risk is substantially higher in patients with CF compared to the general population (1, 2, 5, 9), CF-specific guidelines recommend screening colonoscopy every 5 years starting at the age of 40 years for asymptomatic non-transplant recipients and 30 years for transplant recipients (5).

The three CF patients presented in this article were diagnosed with CRC before the age of 40 years and had no family history of CRC that would have qualified them for earlier screening. While it is true that two of the three patients presented with alarming features (anemia, hematochezia, new-onset abdominal pain, e.g.) that necessitated diagnostic testing, it is clear that these individuals would have benefited from CRC screening practices beginning earlier in life. While CRC screening according to the current existing CF-specific guidelines detects the majority of CF-related CRC, cases such as these should alert clinicians to maintain a high index of suspicion for CRC as early as the third decade of life.

Numerous studies have confirmed a higher risk of early-onset CRC (10, 11) and pre-cancerous adenomas in people with CF (12). In a cohort of CF patients who were screened for CRC, 49% of patients over

the age of 40 had at least one adenomatous polyp, and 23% had at least one advanced adenomatous polyp (13). The study also suggested accelerated polyp formation in the CF population, as evidenced by a high detection rate of new adenomas, including advanced polyps, on serial colonoscopies performed at relatively short intervals. Importantly, the risk of polyp formation varied by genotype, as polyps were more common in those with homozygous F508 mutation and those with CFRD (13). Risk was not predictable based upon gender.

Whether CF represents a hereditary colon cancer syndrome is still under debate (5, 11). On the one hand, CFTR knockout mice have a higher risk of developing rectal hyperplasia and intestinal cancers compared to control groups (14), suggesting that CFTR may play a tumor suppressor role. On the other hand, CF patients receive repeated courses of steroids and antibiotics starting early in their lives, which alter the microbiome and inflammatory milieu of the intestine. CF may therefore predispose patients to bowel cancers through indirect mechanisms (15, 16).

Colonoscopy remains the gold standard test for CRC screening in both the CF and general populations, though CF guidelines recommend a relatively more intensive regimen for bowel preparation, which may be a barrier to compliance (6)**.** Stool-based tests, such as fecal immunochemical testing (FIT) and fecal DNA testing, may also have a role as non-invasive and cost-effective alternatives. Statistical modeling has demonstrated a favorable cost-to-benefit ratio of FIT testing in the CF population, but this approach has not been validated in the clinical setting (17). Despite some potential advantages of FIT over colonoscopy, questions about its practicality remain, such as poor adherence, difficulty with stool collection, follow-up after positive results, and the need for annual testing.

Fecal DNA (fDNA) testing, another non-invasive screening assay, analyzes stool samples for DNA mutations, microsatellite instability, defective DNA mismatch repair, and abnormal DNA methylation, all of which are surrogate markers for abnormal cellular growth (18). The combination of FIT and fecal DNA testing (*Cologuard*, Exact Sciences Corporation, Madison, WI) has demonstrated improved sensitivity for detecting CRC and advanced precancerous lesions when compared with FIT (18, 19). While existing clinical data do not support routinely replacing colonoscopy with FIT or fDNA testing, these non-invasive screening tests may be considered when colonoscopy is deemed unsafe (e.g., in those with end-stage lung disease undergoing transplant evaluation) (7, 20).

## Conclusion

Although CF remains a life-limiting disease, major therapeutic advances have enabled people with CF to live longer. As such, screening for common cancers, especially those for which screening has been shown to save lives, will become increasingly relevant. Published data suggest that pre-cancerous polyps appear earlier and progress to invasive carcinoma more rapidly in CF patients compared to the general population, so current CF-tailored CRC screening guidelines recommend colonoscopy starting at the age of 40 years for asymptomatic individuals. While it is likely that our three patients, all of whom were diagnosed with CRC well below the recommended screening age, would have benefitted from the availability of earlier CRC screening, there are currently no high-level data to support modifying current CRC screening recommendations in CF. Therefore, more robust basic and translational investigations into the mechanisms underlying CF-associated CRC and further clinical studies into the benefits of earlier CRC screening in patients with CF are warranted.

**Conflicts of interests:** None declared.

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