

Colonic Surgery in Patients With Familial Adenomatous Polyposis

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CASE SUMMARY: A 34-year-old woman is referred after a colonoscopy that revealed >100 polyps throughout her colon and rectum (Fig. 1). A random selection of 3 polyps is biopsied and reported as adenomas. She is adopted and is unaware of her biological family. She is found to have a deleterious germline variant in APC (c.1967-1974del). She works as a nurse and is married with 4 children (age: 17, 13, 11, and 6 years). She has had no prior abdominal operations.

CLINICAL QUESTIONS

1. What are the surgical options to treat colonic manifestations of familial adenomatous polyposis (FAP)?
2. What are the extracolonic manifestations of FAP and how should they be managed?
3. What is the appropriate surveillance algorithm for patients with FAP?

BACKGROUND

Familial adenomatous polyposis was the first hereditary colorectal cancer syndrome described. Familial adenomatous polyposis has an incidence of 1/10,000 births, affecting both sexes equally and accounts for <1% of all colorectal cancers. The condition is autosomal dominant

with 100% penetrance, meaning that every patient with a deleterious germline variant in the adenomatous polyposis coli (*APC*) gene will have clinical manifestations of the syndrome. Although extracolonic manifestations of FAP may raise suspicion of the syndrome, the hallmark of FAP is adenomatous polyposis of the large bowel. Patients with a “de novo” (not inherited) mutation typically present with symptoms such as rectal bleeding, diarrhea, abdominal pain, or mucous discharge.

PRESENTATION AND DIAGNOSIS

The first appearance of colonic adenoma in variant carriers is variable, with 15% affected by age 10, 75% by age 20, and 90% by age 30. *APC* is a tumor suppressor gene located on the long arm of chromosome 5(5q21). It is the “gatekeeper” of cellular growth and proliferation signaling. Loss of *APC* function promotes chromosomal instability and drives the adenoma-carcinoma sequence. Without intervention, chromosomal unstable (microsatellite stable) colorectal cancer will typically develop by the fourth decade. The emergence of adenomas and evolution to carcinoma in patients with attenuated FAP is delayed by 10–20 years and has a more proximal distribution.¹

Most patients inherit FAP from a parent and in such patients, genetic testing confirms the diagnosis. De novo *APC* deleterious variants are encountered in 25% of patients diagnosed with FAP syndrome.² A deleterious variant in *APC* can be detected in greater than 80% of patients with phenotypic manifestations of FAP, although the detection rate drops to 56% for those who have 99 to 100 adenomas, 10% for 20 to 99 adenomas, and 5% for 10 to 19 adenomas.³ Up to 60% of patients with de novo mutations are found to have colorectal cancer at presentation.

Patients with greater than 10 cumulative colorectal adenomas should be referred to genetic counseling and they will usually have a genetic panel test.³ Up to 30% of patients with phenotypic features of FAP without an *APC* variant have *MUTYH*-associated polyposis.

Knowing the FAP genotype can aid with phenotype prediction. Deleterious variants in the middle of the gene are more often associated with classic (100–1000 adeno-

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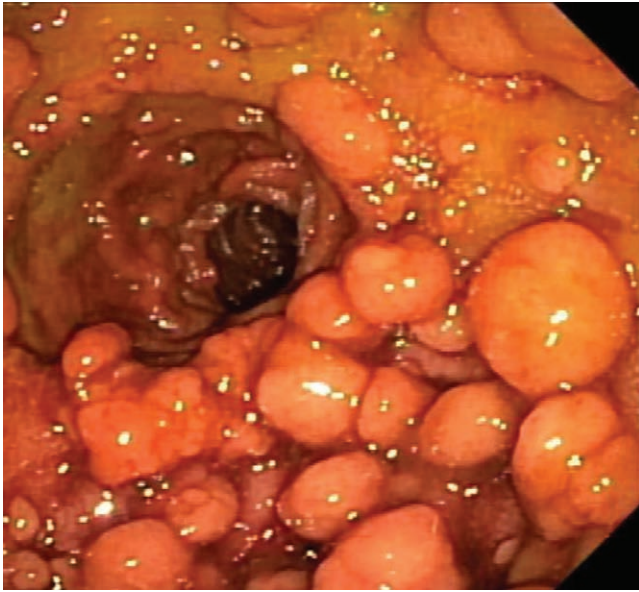


FIGURE 1. Endoscopic view of profuse polyposis.

mas) or profuse (>1000 adenomas) polyposis (Fig. 1).¹ Mutations at the 5' and 3' ends are associated with attenuated FAP (<100 adenomas), and 3' variants are more commonly associated with severe desmoid disease, osteomas, supernumerary teeth, and epidermoid cysts.

Upper GI, desmoid, and thyroid manifestations of FAP are typically encountered by the colorectal surgeon as part of routine screening; other manifestations listed below are encountered less frequently.

Gastric, Ampullary, and Duodenal Adenomas

In the stomach, fundic gland polyps are frequently seen, whereas adenomatous polyps are less common and are typically confined to the antrum. The estimated risk of gastric cancer in Western patients with FAP is 0.6%,¹ although recent reports from the Cleveland Clinic indicate a rising risk⁴ related to pyloric gland adenomas.⁵

Duodenal adenomas are found in >90% patients with FAP, with a 10% lifetime risk of duodenal and ampullary adenocarcinoma.¹ Spigelman classification is used to quantify the number, size, and histology of these adenomas and dictate the need for endoscopic or surgical resection.³ Advanced adenomas (Spigelman stage IV) are best treated by pancreas-sparing duodenectomy, a more conservative and less disruptive option than the classical Whipple procedure.⁶

Desmoid Tumors

Desmoid disease occurs in one-third of patients with FAP and is the second most common cause of death. Desmoid disease can appear as tumors (3-dimensional) or white, mesenteric plaques (2-dimensional). Risk factors for the development of desmoids include genotype, female sex, extracolonic manifestations of FAP, and family history. A desmoid tumor staging system is used to guide therapy.⁷

Thyroid Cancer

Papillary thyroid cancer is seen in up to 2% of patients with FAP, 10 times more frequently than in the general population. Up to 80% of patients with FAP with thyroid cancer demonstrate the cribriform morular variant of papillary thyroid cancer.³ Asymptomatic patients found to have this pathological variant should be referred for colonoscopy.

Adrenal Adenomas

Adrenal tumors are 2 to 4 times more common than in the general population and are seen in up to 13% of patients with FAP.⁸ These tumors are typically "incidentalomas."

Hepatoblastoma

This tumor typically presents in male infants (<6 years of age) and occurs in less than 2% of patients.¹

Brain Tumors

"Turcot syndrome" is an association with colorectal polyposis and brain tumors. This term is confusing, because it has also been attributed to patients with Lynch syndrome who have medulloblastomas. Brain tumors associated with an *APC* mutation are astrocytomas and glioblastomas.⁸

Congenital Hypertrophy of the Retinal Pigment Epithelium

Congenital hypertrophy of the retinal pigment epithelium is the most common extracolonic manifestation of FAP. This is an asymptomatic condition prevalent in 60% of patients, having a 95% specificity for FAP.³ It is therefore an indirect marker in affected kindred.

Other Manifestations

Eldon Gardner described a triad of dental abnormalities, osteomas, and cutaneous cysts in patients with hereditary polyposis. Although the term "Gardner's syndrome" is now historical, the extraintestinal manifestations are predictive of desmoid disease.

MANAGEMENT

Familial adenomatous polyposis is not cured by proctocolectomy. The aim of prophylactic colonic resection is to prevent colorectal adenocarcinoma, while maintaining a quality of life as close to normal as possible. The choice and timing of resection is primarily determined by the adenoma burden, although factors associated with the development and progression of desmoid disease are considered.

Prophylactic surgery is typically planned for late teens or early twenties. Indications for early surgery include rapid growth in size, or number of adenomas (>10 mm), high-grade dysplasia, and symptomatic disease.⁹ Rectal sparing surgery has been demonstrated to be safe in patients with <20 rectal polyps and <1000 synchronous

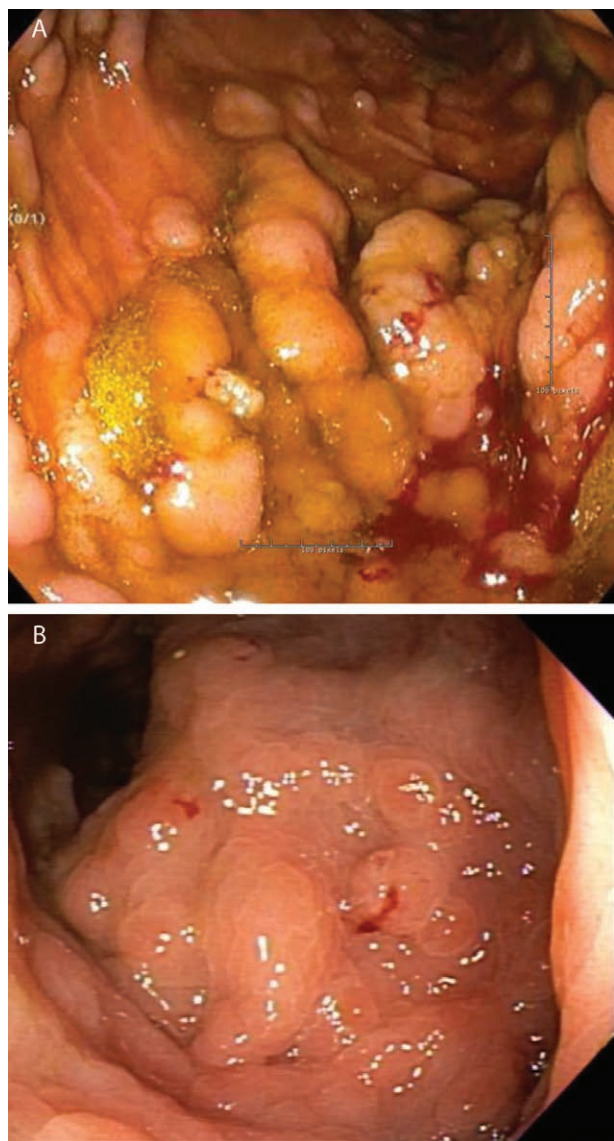


FIGURE 2. Photo of (A) pouch body polyposis and (B) pouch body with lymphoid follicles.

adenomas.³ High-volume centers may use a combination of aggressive polypectomy, chemoprevention, and frequent surveillance in an attempt to preserve the rectum in highly selected cases.

The 4 surgical options include: proctocolectomy and end-ileostomy, proctocolectomy and stapled IPAA, proctocolectomy and handsewn IPAA with mucosectomy, or total colectomy and ileorectal anastomosis (IRA). Data suggest that laparoscopic IRA is the least “desmoidogenic” surgical option. Desmoid disease can prevent formation of IPAA in patients with a prior IRA in about 15% of cases.

Provided the rectal cuff is polyp free, evidence does not support routine mucosectomy.⁹ The lower incidence of adenoma after handsewn IPAA with mucosectomy (23%), compared to stapled IPAA (51%),¹⁰ comes at the price of significantly poorer function. Cancer has been de-

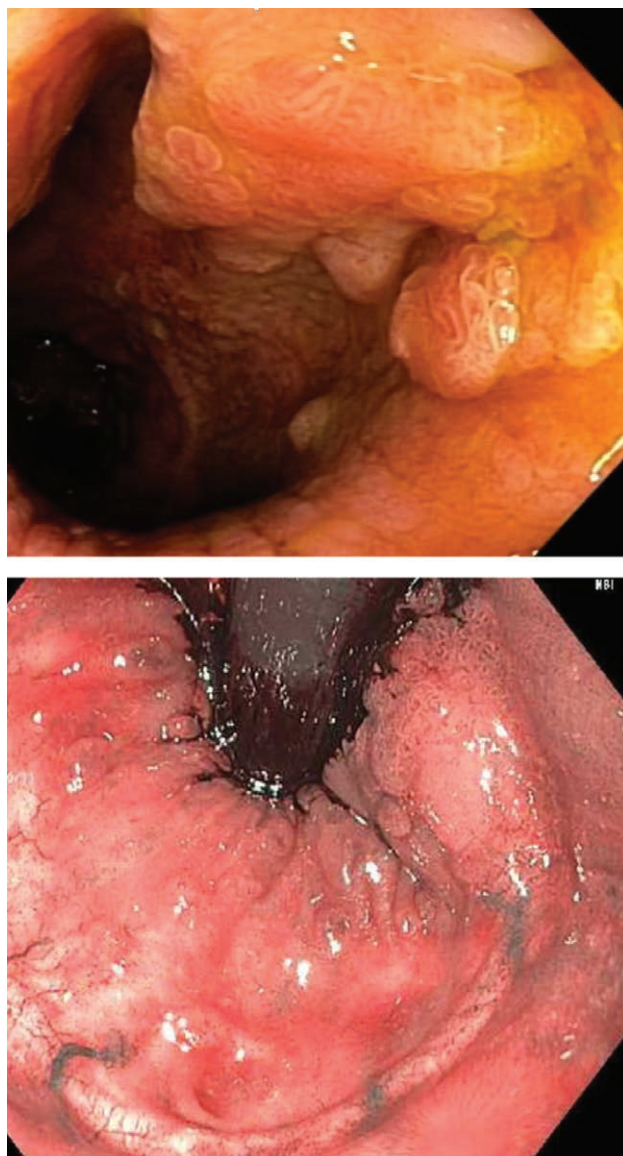


FIGURE 3. Photo of adenomas at the anal transitional zone (ATZ) seen via endoscopy.

scribed following mucosectomy and the residual nests of rectal mucosa are present in up to 21% of patients.¹¹

Delaying surgery may be appropriate in selected asymptomatic patients, notably those with a high risk of desmoids, and in young women, because pelvic surgery decreases fecundity.¹² The preferred mode of delivery in pregnant patients with FAP, in particular, with an IPAA is unclear. Such patients have the highest risk of developing desmoids following abdominal surgery, yet would be catastrophically affected by an anal sphincter injury.

Screening

Screening should be performed in accordance with the National Comprehensive Cancer Network guidelines.³ Patients with a positive genotype are screened yearly with colonoscopy, starting at age 10 to 12. At-risk children in

families without a genotype can be screened with flexible sigmoidoscopy, changing to colonoscopy when adenomas are found. Screening for gastric and duodenal adenomas begins at age 20 to 25. Screened for papillary thyroid cancer is currently performed yearly, although there are some recent data that less frequent assessment may be appropriate.

Surveillance

Following a total colectomy and IRA, the rectum and 15 cm of distal ileum are checked yearly. Polyps <5 mm should be counted, but do not need to be removed provided the patient is compliant with surveillance. Large polyps should be removed, and areas of flat mucosal abnormalities should be removed or at least biopsied.

Following IPAA, screening with yearly pouchoscopy is essential. In some patients, a lubricated pediatric endoscope may be better tolerated than an adult scope, because of anastomotic narrowing. In young patients, lymphoid follicles may be present in the pouch body and afferent limb of ileum, and can be mistaken for adenomas (Fig. 2).

Superficial ulceration at the staple line of the pouch body may be seen. This is not associated with IBD.

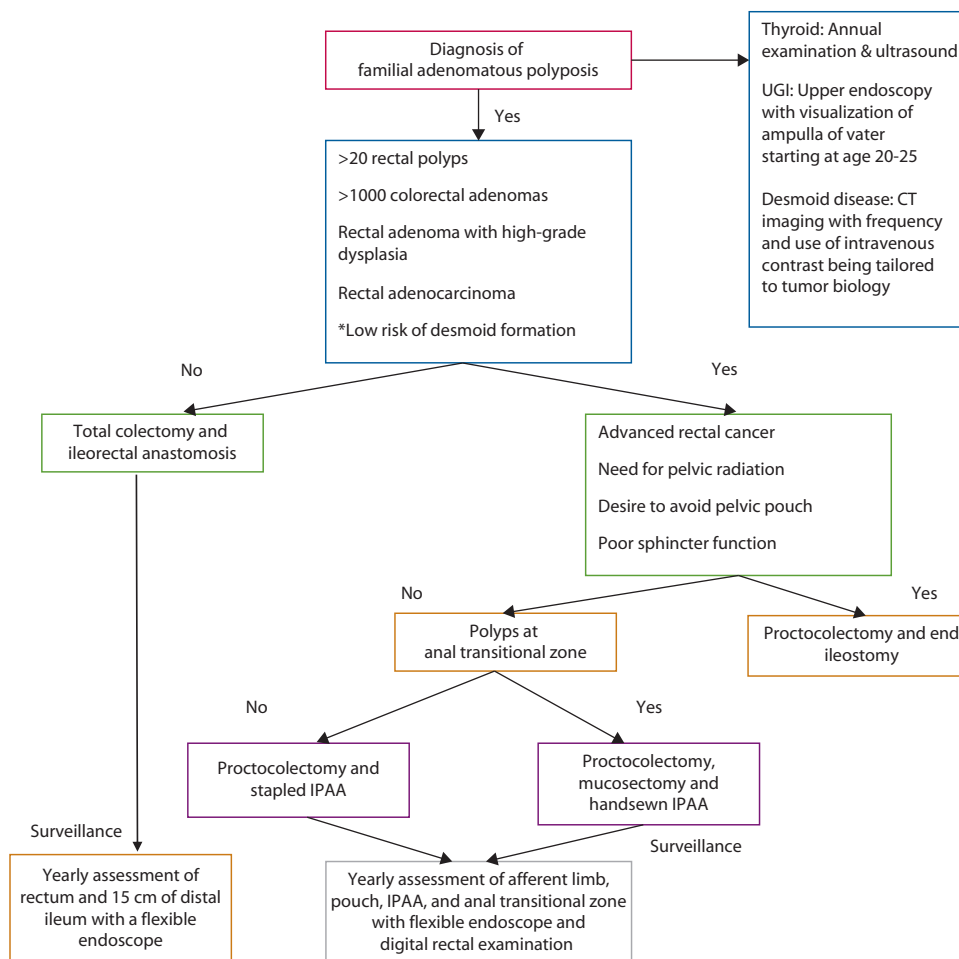
Specific attention is directed toward the anal transitional zone (ATZ) and anus. ATZ polyps are common after stapled IPAA and can even occur after an apparent mucosal “stripping.” Left alone, these polyps can progress to cancer. Isolated polyps in the ATZ are resected with endoscopic snare, or via a transanal approach. The management of circumferential polyposis at the ATZ is complex, depending on the length of the retained ATZ and the extent of its involvement with adenoma (Fig. 3). A mucosal strip can be performed, which should be restricted to less than 50% of the anal circumference per intervention. A 1-cm stricture in the anal canal can usually be tolerated, but longer strictures can affect defecation.

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EVALUATION AND TREATMENT ALGORITHM

Based on *Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes*, Herzig et al.⁹



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Expert Commentary on Colonic Surgery in Patients With Familial Adenomatous Polyposis

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Familial adenomatous polyposis presents 3 major challenges to colorectal surgeons. The first is to protect patients from the risk of cancer and desmoid tumors in the least invasive, least intrusive, and safest way possible. This involves a carefully planned strategy of care, taking into account the differences in risk, the implications of various surgical options in the individual patient, and the likely effect of interventions on quality of life. The second is to manage the ongoing risk of neoplasia by a commitment to lifelong surveillance that involves specialists in multiple disciplines. Effective surveillance requires a partnership between patient and physician where both

commit to a program based on published guidelines that are amended according to individual needs. The third is to extend care to the family, which involves education and counseling, emotional and sometimes psychological support, while addressing wide-ranging concerns that may include ethics, genetics, finances, employment, and palliative care. It is obvious that such patients and families are ideally managed in the context of a dedicated center or registry. Colorectal surgeons who take on these patients must make themselves aware of the nuances of the syndrome that affect surgical decision making. The case presented here is a good example.

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