

# Familial Polyposis Coli:

## Clinical Manifestations, Evaluation, Management and Treatment

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### Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant, hereditary colon cancer syndrome that is characterized by the presence of innumerable adenomatous polyps in the colon and rectum. Gardner's syndrome is a variant of FAP, which in addition to the colonic polyps, also presents extracolonic manifestations, including desmoid tumors, osteomas, epidermoid cysts, various soft tissue tumors, and a predisposition to thyroid and periampullary cancers. Mutations of the *APC* gene are thought to be responsible for the development of FAP, and the location of the mutation on the gene is thought to influence the nature of the extracolonic manifestations that a given patient might develop. Though patients are often asymptomatic, bleeding, diarrhea, abdominal pain and mucous discharge frequently occur. Diagnostic tools include genetic testing, endoscopy, and monitoring for extra-intestinal manifestations. Currently, surgery is the only effective means of preventing progression to colorectal carcinoma. Restorative proctocolectomy with ileal pouch anal anastomosis (RPC/IPAA) with mucosectomy is the preferred surgical procedure, since it attempts to eliminate all colorectal mucosa without the need for an ostomy. Periampullary carcinoma and intra-abdominal desmoid tumors are a significant cause of morbidity and mortality in these patients after colectomy. Frequent endoscopy is needed to prevent the former, while there is no definitive treatment available yet for the latter. The following article presents a case and reviews the evaluation, management and treatment of Gardner's syndrome.

**Key Words:** Gardner, familial adenomatous polyposis, hereditary colon cancer, desmoid tumors.

### Case Report

THE PATIENT WAS A 39-YEAR-OLD FEMALE with a two-month history of intermittent rectal bleeding. She reported no symptoms of weight loss, anorexia, or abdominal pain. Her family history included several individuals on her mother's side (maternal uncle and several cousins) with colon cancer during their third and fourth decades of life. The patient had been told that they had "Gardner's syndrome," but she was unaware that she was also at risk. The patient was afebrile with normal vital signs. Her abdomen was soft, nontender and nondistended, and had hypoactive bowel sounds. Her rectal examination was negative. Her complete blood count (CBC) was significant for anemia, with a hematocrit of 28. On colonoscopy, she was found to have numerous

polyps carpeting the entire colon and rectum, which was consistent with familial adenomatous polyposis (FAP). An upper endoscopy was negative. A CT scan did not reveal any desmoid tumors, and a small bowel series revealed no abnormalities. She underwent a restorative proctocolectomy with mucosectomy and ileal-pouch/anal anastomosis. Pathology of the specimen confirmed the diagnosis of familial adenomatous polyposis (Figs. 1 and 2). There was no evidence of cancer. On discharge, it was recommended that all family members be evaluated for FAP.

### Introduction

Each year, approximately 148,300 individuals are diagnosed with colon cancer; 56,500 cases will result in death (1). Nearly 5–10% of colon cancers are autosomal dominant and follow a Mendelian pattern of inheritance. The two major forms of hereditary colon cancer are hereditary nonpolyposis colorectal cancer (HNPCC) and FAP. The following discussion will briefly review FAP and focus on Gardner's syndrome, a variant of FAP with characteristic extracolonic manifestations.

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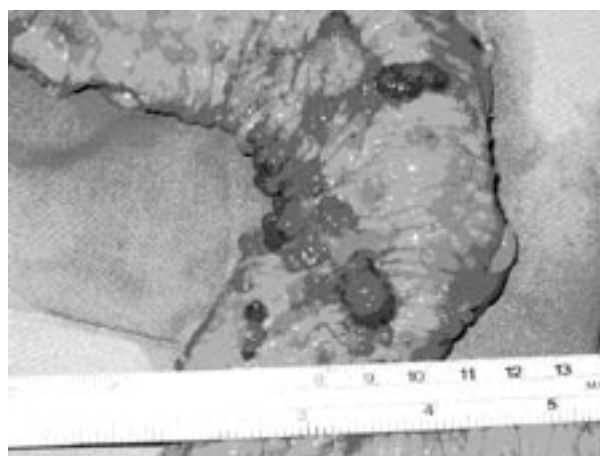
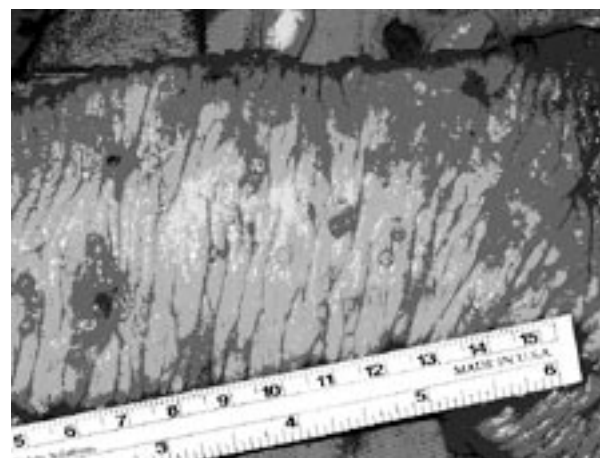
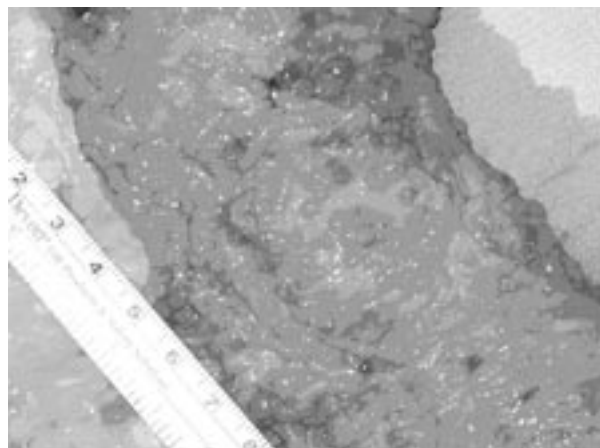


**Fig. 1.** The entire colectomy specimen. From a distance, the left colon appears to be less involved than the right side.

### FAP

FAP is an autosomal dominant disease of the colon characterized by the presence of innumerable adenomatous polyps. The incidence of this disorder is between 1 in 8,300 and 1 in 14,025 live births, affecting both genders equally, with a uniform worldwide distribution (2). Without colectomy, the development of colorectal cancer is inevitable and is thought to occur approximately 10–15 years after the onset of polyposis (3, 4). The average age at diagnosis is 34.5–43 years and the average age at diagnosis of colorectal cancer is 39 years (3–5). The genetic defect in FAP has been linked to germline mutations of the *APC* gene on chromosome 5q21 (6). *APC* is a tumor-suppressor gene and has a putative role in cell adhesion, signal transduction and transcriptional activation (7).

Patients are usually asymptomatic prior to the appearance of polyps, which start to develop at puberty. Polyposis continues into adulthood until the entire colon is carpeted with adenomas. The histology of polyps seen in FAP



**Fig. 2.** Close-up view of the mucosal aspect of the sigmoid colon, showing numerous adenomatous polyps throughout.

is similar to that of sporadic polyps and displays tubular, villous and tubulovillous characteristics. The cancer risk is thought to be a function of the number of the polyps found in the colon (8). On average, 1000 macroscopic polyps are noted to be present on diseased specimens, with tens of thousands of polyps less than 1 cm in diameter (Figs. 1 and 2).

## Genetics

The gene responsible for FAP, the *APC* gene, is a large gene with more than 1400 different reported mutations (9–11). The mutated *APC* allele is inherited as a germline mutation from the affected parent. Interestingly, however, adenomas develop only when the second allele (inherited from the unaffected parent) mutates or is inactivated (12). The pathway controlled by the *APC* gene includes *c-myc* and *beta-Catenin* as downstream targets and appears to impact kinetochore and microtubule attachment.

The *APC* protein is a multifunctional regulator of colonic epithelial cell renewal. In addition to its role as a tumor suppressor protein, it regulates cellular proliferation, differentiation, migration and apoptosis. Mutations in *APC* interfere with the way epithelial cells divide and distribute their nuclear DNA (13). Since most *APC* mutations result in deletions of the carboxy terminal, this domain is considered to carry the tumor suppressor function (14).

In FAP, a clear correlation between the specific clinical features and the location of the mutation on the *APC* gene (termed the genotype-phenotype correlation) has been observed (15). For example, an increased risk of desmoid tumors is associated with mutations between codons 1445 and 1578. Similar correlations have been made between congenital hypertrophy of pigmented retinal epithelium and attenuated FAP (16, 17). These correlations are not yet uniform, and their current value lies in their ability to direct screening and diagnostic testing.

Prior to identification of the *APC* gene, a number of variants of FAP had been described, based on different extracolonic manifestations. With the information we currently have, it is believed that many of these syndromes merely reflect the variety of locations of mutations on the *APC* gene. These syndromes include Gardner's syndrome (multiple osteomata, cysts and soft tissue tumors), Turcot's syndrome (FAP in association with malignant tumors of the central nervous system), Cronkhite-Canada syndrome (gastrointestinal polyposis, skin hyperpigmentation, alopecia and nail dystrophy), and attenuated FAP or AFAP (<100 colonic adenomas with right-sided predominance) (18, 19).

## Gardner's Syndrome

When FAP is associated with desmoid tumors, mesenteric fibromatosis, dental abnormalities, gastric polyps, duodenal polyps, lym-

phoid hyperplasia of the terminal ileum and ileal adenomas, it is called Gardner's (or Gardner) syndrome. The syndrome, first described in 1951, was initially thought to be an entity of its own (20).

## Clinical Manifestations

The most common symptoms related to the polyposis are bleeding, diarrhea, abdominal pain and mucous discharge. Weight loss, anemia and intestinal obstruction imply the presence of cancer, and an estimated 25% of patients with the syndrome have colorectal cancer at diagnosis (21).

An often-lethal complication of FAP is diffuse mesenteric fibrosis or desmoid tumors. Their reported incidence among patients with Gardner's syndrome is 3.5–5.7% and they commonly manifest 1–3 years following surgery (22, 23). These neoplasms usually arise in abdominal incisions, the abdominal cavity or the retroperitoneum (24, 25). Some authors regard desmoid tumors as the most troubling consequence of Gardner's syndrome. Extensive small bowel resection secondary to obstruction and urinary obstruction are common complications of desmoid tumors. Death is usually secondary to intestinal obstruction or vascular occlusion (26, 27). Among patients with FAP, desmoid tumors have a high recurrence rate and are only resected when symptomatic. In a series reported by Jones et al., 50% of patients had complications (intestinal obstruction, hydronephrosis and fistulas) and 2 of the 9 deaths were attributed to desmoid tumors (27). Since desmoid tumors are a common cause of morbidity and mortality in this population, various treatment options have been investigated (see "Management of Desmoid Tumors," below).

Since the *APC* gene is a germline mutation, tumors develop in various extracolonic sites, including thyroid and adrenal glands, liver, duodenum and pancreas (28–31). Periampullary carcinoma (carcinoma of the duodenum, ampulla of Vater or pancreas) has been strongly associated with Gardner's syndrome. Research at St. Mark's Hospital, London, indicated a 12% incidence of periampullary cancer in a series of patients 5 years after colectomy (22). Similar associations have been reported by Sugihara (32). It is strongly recommended that patients with Gardner's syndrome or FAP undergo frequent upper gastrointestinal endoscopy and radiological studies looking for abnormalities in these other extracolonic sites.

Epidermoid cysts are common benign findings in the general population and are thought to occur more frequently among patients with Gardner's syndrome. Since they are usually uncommon prior to puberty, their presence prior to puberty should alert the physician to evaluate the colon and the rectum for polyps (22, 33).

Osteomas in relation to Gardner's syndrome are typically found in the skull and mandible, and might be the only extracolonic manifestation related to the disease (34, 35).

Asymptomatic pigmented ocular fundic lesions are present in more than 90% of patients with FAP or Gardner's syndrome (36). It has been suggested that the presence of congenital hypertrophy of the retinal pigment epithelium, if demonstrated in relatives, is almost 100% predictive of FAP (37).

The Table lists some of the extracolonic symptoms that have been described in association with FAP (18, 19).

## Evaluation

As in any disease with a strong genetic component, an extensive family history is useful in establishing the diagnosis. A combination of endoscopy, genetic testing and observation of extracolonic manifestations is used in the diagnosis of FAP and Gardner's syndrome.

Genetic testing is the most efficient mode of identifying gene carriers in a FAP relative. In cases where the exact sequence of a mutation is known in one family member, direct sequencing directed at the region of the *APC* gene thought to be affected has been shown to be 90% cost effective and accurate (38). Linkage analysis to markers on chromosome 5q, protein truncation testing, direct sequencing, conformation-sensitive gel electrophoresis, and single-strand, conformation-sensitive gel electrophoresis all have accuracies between 70% and 90% (39).

Screening colonoscopy should begin at age 10–12 years for patients who are known to have *APC* mutations (19). Individuals who are at risk with an unknown mutation status should have screening colonoscopies by age 15, every year from age 26–35, every other year from age 26–35, and every three years from age 36–50.

Although there are no clear guidelines for upper endoscopy, all patients should have forward-viewing extended and side-viewing upper tract endoscopies (40–42). Duodenal polyps > 0.5–1 cm should be removed and the follow-up interval should be based on the histology of the polyp. Polyps that are villous or harbor high-grade dysplasia should have follow-ups every 2–3 months until ablation is achieved. When polyps carpet the mucosa or when complete ablation is not achieved endoscopically, surgical intervention is required. Ampullary polyps > 2 cm should be removed with surgical resection (41, 42).

An annual physical examination to screen for thyroid cancer is warranted. Liver ultrasonography and serum alpha-fetoprotein are being investigated as possible screening tests for hepatoblastoma.

## Medical Management

The chemopreventive drugs used most extensively for patients with FAP have been the cyclo-oxygenase inhibitors. Some studies have reported a regression of polyps and biochemical markers after the use of these agents. However, primary chemoprevention of colorectal adenomas was not achieved in FAP patients treated with sulindac (43, 44). The use of cyclo-oxygenase inhibitors in conjunction with ursodeoxycholic acid is being studied for its effect on duodenal polyps, ileal pouch polyps, and desmoids. Vitamin C, vitamin E, and supplemental wheat fiber have not had a clinically sig-

**TABLE**

*Benign and Malignant Lesions Associated with Familial Adenomatous Polyposis*

| <b>Malignant Tumors (lifetime risk)</b>  | <b>Other Lesions</b>                 |
|--|--------------------------------------|
| Duodenal (5–11%)                         | Nasopharyngeal angiofibromas         |
| Pancreatic (2%)                          | Osteomas                             |
| Thyroid (2%)                             | Radiopaque jaw lesions               |
| Brain (medulloblastoma) <1%              | Supernumerary teeth                  |
| Hepatoblastoma (0.7% of children < 5yrs) | Lipomas, fibromas, epidermoid cysts  |
|  | Desmoid tumors                       |
|  | Gastric adenomas/fundic gland polyps |
|  | Duodenal, jejunal and ileal adenomas |

nificant impact on the appearance or progression of polyps (12).

### Surgical Management

Surgery is the only effective therapeutic option currently available to prevent progression to colorectal cancer. The chief considerations are the timing and the extent of surgery. The general recommendation is that prophylactic colectomy should be performed by the late teens in patients for whom the diagnosis of FAP is made.

The current surgical options include the following:

1. Total proctocolectomy (TPC) with ileostomy.
2. Restorative proctocolectomy with ileal pouch anal anastomosis (RPC/IPAA) with mucosectomy.
3. RPC/IPAA using double staple technique.
4. Total abdominal colectomy with ileorectal anastomosis (IRA) with rigorous surveillance of the rectal remnant.

TPC with ileostomy carries the disadvantage of a permanent ileostomy, which can be a severe drawback to a young patient in his/her teens. This procedure is only done when a proctocolectomy is required and there is a contraindication to performing an IPAA.

Options 1 and 2 are preferred because they attempt to eliminate all colon and rectal mucosa, thereby assuring that these patients have the lowest risk of developing colorectal cancer. An RPC/IPAA with mucosectomy restores bowel continuity and attempts to eliminate all rectal tissue and subsequent cancer risk. The disadvantage of RPC/IPAA with mucosectomy is that this operation is reported by some authors to be technically more difficult (45, 46). TPC with ileal pouch-anal anastomosis, including mucosectomy to the dentate line, has been the preferred approach at the Mayo Clinic. They have reported a low postoperative complication risk and satisfactory functional results of the ileal pouch (36, 47–49).

Some authors suggest that islands of rectal mucosa might be retained, even with mucosectomy. Reports have indicated that the risk of dysplasia and polyp formation is decreased but not eliminated (50–52). The Cleveland Clinic group reported that a stapled anastomosis offers a better functional outcome and might prevent the need for a diversion. However, they recommend that this superior outcome should be balanced against a 28% increase in the incidence

of adenomas in the anal transitional zone (51). If a transitional zone neoplasia is found on surveillance after a stapled anastomosis, the transitional zone can be stripped transanally and the pouch advanced to the dentate line (53).

Experience with total abdominal colectomy with IRA is largely from the Cleveland Clinic and St. Marks groups (54, 55). The Cleveland Clinic protocol included colectomy by age 20, anastomosis at 12 cm from the dentate line, and follow-up every 6 months. Some authors have argued that colectomy might lead to the spontaneous regression of polyps, but the permanence of this regression is questionable (56–59). Of a group of 89 patients studied by the Mayo group, two developed rectal cancer. However, since the center adhered to rigorous follow-up care, the cancers were identified at an early stage (36). It is argued that the risk of rectal cancer is related to the number of polyps. IRA might therefore be an appropriate choice for patients with attenuated FAP or relative rectal sparing (<20 rectal adenomas, 1,000 colonic adenomas) (50).

The surgical options must be tailored to the needs of the individual patients and their reliability to maintain follow-up care. A review of 115 patients with FAP at Mount Sinai Medical Center revealed that one out of four patients with ileorectal anastomosis developed rectal cancer at a mean follow-up time of 13 years (60). This study also suggested that rectal cancer in these populations tends to be advanced tumors. Therefore, excision of the entire colorectal mucosa is considered to be the treatment of choice. Similar recommendations have been reported at other institutions (61–63).

In light of these factors, the preferred procedure for most patients with FAP is an RPC/IPAA with mucosectomy. Moreover, any surgical procedure that restores intestinal continuity must be followed up with rigorous surveillance. A mucosectomy does not eliminate the risk of malignancy and should by no means offer a false sense of security.

The development of adenomas within the ileal pouch several years after the surgery is a well-recognized phenomenon. However, the natural history of ileal adenomas and their risk for progression to cancer is incompletely characterized (36).

### Management of Desmoid Tumors

Since desmoid tumors are a cause of significant morbidity and mortality in this popula-

tion, the management of desmoid tumors requires special attention. A strong family history of desmoid tumors and a high-risk location of the mutation on the *APC* gene increase the risk for the development of desmoid tumors. Due to a reported 85% recurrence rate of desmoid tumors after surgical excision, surgery should be performed only when absolutely necessary. Some reports have suggested that abdominal wall desmoids respond more favorably to surgical resection because they are often encapsulated (64–66). The presence of desmoid tumors might favor an IPAA over an IRA, because IRA might require additional surgery in the future.

Tamoxifen, toremifene, and sulindac have been used as treatments, but the results have not been promising. Reports have suggested that therapy might be associated with an initial benefit but the long-term clinical improvement is minimal (65–71). Cytotoxic chemotherapy (doxorubicin, dacarbazine, and carboplatin) may be effective in treating aggressive, rapidly growing and unresectable intra-abdominal desmoids. Significant side effects include febrile neutropenia, nausea, vomiting, stomatitis, thrombocytopenia and epistaxis (72, 73). Radiation therapy might be effective in some cases but frequently carries complications (74).

Intra-abdominal desmoid tumors usually involve the mesentery and often involve the mesenteric vessels. They invade the mesentery diffusely, kink loops of bowel and can obstruct the ureters. Large and complex resections are required and recurrence is very common. Surgery is usually reserved as a last resort for intra-abdominal desmoids. The presence of desmoids might prevent the construction of a pouch and might require the creation of a permanent ileostomy (75–77). The management of intra-abdominal desmoid tumors is complex and is dependant on their clinical behavior. Based on the American Society of Colon and Rectal Surgeons Guidelines, slow-growing and inert intra-abdominal desmoids should be treated with sulindac or not treated at all. Desmoids that are growing slowly or are mildly symptomatic can be treated with sulindac and tamoxifen or with vinblastine and methotrexate, since these regimens are less toxic. Aggressive desmoids are treated with antisarcoma chemotherapy such as doxorubicin and dacarbazine. Intestinal transplant has been attempted to rescue FAP patients with desmoid tumors (78).

Surgical therapy is favored for abdominal wall desmoid tumors, since they are easier to

excise than intra-abdominal desmoid tumors, recurrence rates are lower, and morbidity associated with the procedure is less. The excision should be completed with a 1 cm margin. A mesh can be used to cover the defect if required (50).

## Conclusion

FAP is an autosomal dominant, hereditary colon cancer syndrome that is characterized by the presence of innumerable polyps in the colon and rectum. Gardner's syndrome is a variant of FAP characterized by extracolonic manifestations, including desmoid tumors, osteomas, epidermoid cysts, various soft tissue tumors, and a predisposition for thyroid and periampullary cancers. Diagnostic tools include genetic testing, endoscopy, and monitoring for extra-intestinal manifestations. Currently, surgery is the only effective means of preventing progression to colorectal carcinoma. RPC/IPAA with mucosectomy is the preferred surgical procedure for these patients, as it attempts to eliminate all colorectal mucosa. In addition, aggressive surveillance is required to decrease the morbidity and mortality from the various extracolonic manifestations. Periampullary carcinomas and desmoid tumors are significant causes of morbidity and mortality in these patients. Frequent endoscopy is needed to prevent the former, while there is no definitive treatment available yet for the latter. In an effort to improve research, education, and medical and follow-up care, a number of registries have been set up for high-risk families (36).

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