FAMILIAL ADENOMATOUS POLYPOSIS (FAP): WHAT MUST BE KNOWN AND WHAT SHOULD BE DONE – CASE REPORT

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Abstract

Familial adenomatous polyposis (FAP) is a neoplastic disorder of major concern to pediatric surgeons due its fatal adenoma-carcinoma sequence. This case report illustrates the attempt of surgery to alter and perhaps break such a sequence.

Key words: familial adenomatous polyposis (FAP), APC gene, extracolonic cancer.

Introduction

Familial adenomatous polyposis (FAP), also known previously as adenomatous polyposis coli (the latter term is being now reserved for the relevant gene), albeit a rare condition, is the most common adenomatous polyposis syndrome. It is classically characterized by the early onset of hundreds to thousands of polyps disseminated throughout the colon. FAP is an important neoplastic disorder since it invariably evolves into carcinoma of the colon by the fifth decade of life if left untreated (adenoma-carcinoma sequence.)

It has an autosomal dominant pattern of inheritance due a germline mutation in the adenomatous polyposis coli (APC) tumor suppressor gene, located on band 5q21.

The incidence of FAP is constant worldwide and ranges from 1 in 6.000 to 1 in 12.000 births, with both sexes being equally involved.

Classification and natural history

Different mutations in the APC gene define a spectrum of conditions known as APC-associated polyposis which include: (1) FAP, (2) Gardner and Turcot syndrome as overlapping variants with extracolonic manifestations, and (3) Attenuated FAP (AFAP) (or Flat adenoma syndrome.)

1. CLASSIC FAP: is diagnosed clinically in an individual with over 100 colorectal adenomatous polyps; or fewer than 100 adenomatous polyps and a relative with FAP. Up to several thousands have been described and the mean is 500 polyps at the time of diagnosis. The median ages for patients to develop polyps is 16, for bowel symptoms 29 and for colorectal carcinoma is 36 years.

2.1. GARDNER SYNDROME (GS) is the association of colonic adenomatous polyposis, osteomas (mainly on the skull and mandible), dental abnormalities (Unerupted teeth, congenital absence of one or more teeth, supernumerary teeth, dentigerous cysts, and odontomas), and soft tissue tumors (epidermoid cysts, fibromas, desmoid tumors). These benign extraintestinal growths occur in about 20% of individuals and families with FAP.

2.2. TURCOT SYNDROME (TS) is a rare combination of multicentric colonic adenomatous polyposis and CNS tumors, usually medulloblastoma. Patients develop colorectal carcinoma in young adulthood from malignant transformation of the precancerous lesions or may arise de novo in the intact intercalated epithelium.

3. AFAP as the term implies is considered in an individual with fewer adenomatous polyps averaging 30 and with a more proximal colonic distribution when compared to classic FAP. The median ages to develop polyps is 36 and for colorectal carcinoma is 50-55 years (10-15 years later than patients with classic FAP, but earlier than those with sporadic colorectal carcinoma.)

Gastric polyps and adenomatous polyps of the small intestine are being increasingly detected with appropriate upper gastrointestinal endoscopy.

No correlation could be established between the number of colonic polyps and the frequency of upper gastrointestinal polyps. If gastric polyps are considered to have a minimal malignancy potential, the lifetime risk of small intestine malignancy is 4-12%; being the second most common malignancy in patients with FAP. The majority of small intestine carcinoma occur in the duodenum (mainly in the periampullary region, including the duodenal papilla and ampulla of Vater.) (Table 1).

Table 1 - Upper gastrointestinal polyps in FAP.

	Gastric polyps		Polyps of the small intestine	
Histology	hamartomatous fundic-gland	adenomatous	adenomatous	
Location	fundus + body	antrum	D II + D III	periampullary region
Frequency in FAP	50 %	10 %	50-90 %	50 %

Diagnosis - tools of the trade

History and physical exam

- 80% of patients with FAP have a family history of polyps and/or colorectal cancer at age 40 years or younger.
- Most patients are asymptomatic until colorectal carcinoma develops. Symptoms when present include non-specific abdominal pain, a palpable abdominal mass or palpable mass on rectal examination in a young patient, change in bowel habits, a progressively installed chronic bloody diarrhea and unexplained rectal bleeding.
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE), best detected by slit-lamp examination. These are minimal flat pigmented lesions of the retina, mostly multiple and bilateral, that are highly specific for FAP.

Differential diagnosis

Peutz-Jeghers Syndrome
Bannayan-Riley-Ruvalcaba syndrome
Cowden disease
Juvenile polyposis syndrome
Cronkhite-Canada syndrome
Hereditary nonpolyposis colon cancer
Hyperplastic polyposis
Nodular lymphoid hyperplasia
Lymphomatous polyposis
Neurofibromatosis type 1 (NF-1)
Inflammatory polyposis
MYH-associated polyposis

Lab studies

CBC - chronic bloody diarrhea and rectal bleeding are often associated with anemia.

Proteinemia- late manifestations of FAP include protein-losing enteropathy and malnutrition.

Alpha-fetoprotein (AFP).

Imaging studies

- Barium studies, flexible sigmoidoscopy, colonoscopy (usually reserved for AFAP because of the proximal colonic distribution of the polyps), front and side-viewing esophagogastroduodenoscopy when FAP is established (in order to visualize gastric, duodenal, and periampullary adenomas.)
- Dental panoramic and skull x-ray films to detect osteomas and dental abnormalities encountered in Gardner syndrome.
- Periodic abdominal ultrasounds and CT scans to detect intra-abdominal desmoid tumors and pancreatic cancer.

Genetic studies

APC gene sequencing
In vitro protein synthesis assay
Linkage testing

Histology

Tubular adenomatous polyps predominate, and later tubulovillous adenomas may be detected as they increase in size.

Surgical treatment and long - term management

(1) Proctocolectomy with permanent abdominal wall ileostomy.
(2) Proctocolectomy with ileal pouch-anal anastomosis/IPAA (restorative proctocolectomy) and temporary diverting ileostomy.
(3) Subtotal colectomy and ileoproctostomy, with repeated postoperative proctoscopy at 3-6 month intervals for fulguration of residual and subsequent rectal polyps.
(4) Subtotal colectomy and rectal mucosectomy with or without a temporary diverting ileostomy and an endorectal pouch reservoir.

The ideal surgery for a benign disease with an inevitable malignant transformation is prophylactic resection of all potentially malignant tissue. If this ideal is fulfilled by proctocolectomy, aggressive pelvic dissection may leave the patient with serious sequelae (neurogenic bladder, male impotence, female infertility.) On the other hand, leaving the rectum in place requires perseverant monitoring of residual and subsequent rectal polyps, with no permanent assurance to avoid rectal carcinoma.

Regression of residual rectal polyps, in terms of number and size, has been described after ileoproctostomy with or without the use of NSAIDs (Celecoxib, Sulindac or Indomethacin.)

Complications and prognosis

If left untreated patients with FAP have a median life expectancy of 42 years. It is true that colectomy extends such a short life expectancy, but since surgery only neutralizes the risk of colorectal carcinoma at best, continuous monitoring of patients for developing extracolonic cancers cannot be overemphasized. (Table 2).

Desmoid tumors (diffuse mesenteric fibromatosis), concerning about 20% of patients with FAP, typically postcolectomy.

The cumulative risk for developing extracolonic cancer, mostly periampullary tumors, is 11% by age 50 years and 52% by 75 years.

Table 2 - Lifetime Risk of Extracolonic Cancer in FAP.

Site	Type of Cancer	Risk of Cancer
Small intestine: duodenum or periampulla	Carcinoma	4-12%
Small intestine: distal to the duodenum		Rare
Stomach	Adenocarcinoma	0.5%
Pancreas		~2%
Thyroid	Papillary thyroid carcinoma	~2%
CNS	Usually medulloblastoma	<1%
Liver	Hepatoblastoma	1.6% (children <age 5 years)
Bile ducts	Adenocarcinoma	Low, but increased
Adrenal gland		

CASE REPORT

History and physical exam

13 y.o. male patient with a known family history of FAP and colorectal cancer**.** (Figure 1).

The patient sought medical attention because of recurrent abdominal pain and diarrhea over the last 4 months. The physical exam outlined a non-specific diffuse abdominal pain, both spontaneous and on palpation, with no palpable abdominal mass and no clinical sign of peritoneal involvement. Likewise, there was no palpable mass on rectal examination and no bleeding.

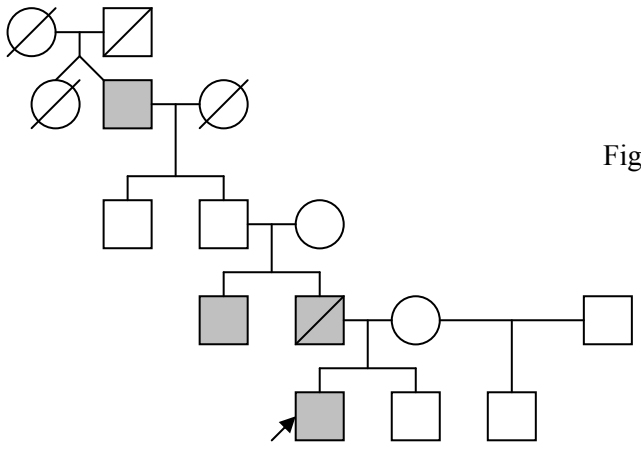

Figure 1 - Pedigree analysis.

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Lab studies
CBC – normal counts.
Proteinemia – normal value.
Alpha-fetoprotein (AFP) – matched value for age.

Imaging studies
- Barium study of the abdomen showed multiple polyps disseminated throughout the colon. (Figure 2)

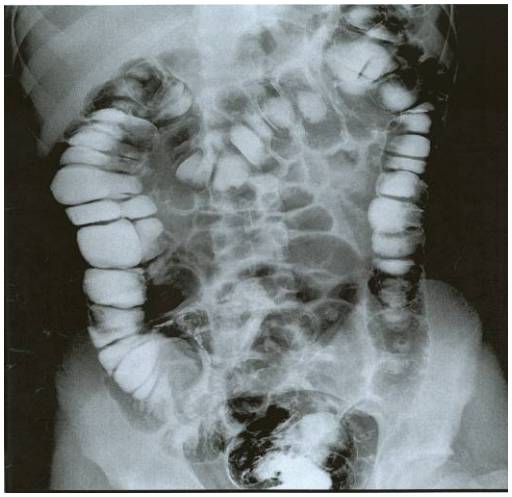


Figure 2. Barium study - multiple polyps disseminated throughout the colon.

- Colonoscopy detected hundreds of sessile polyps involving the entire colon extending from the rectum up to the cecum and hence establishing the diagnosis of FAP.
- Upper G.I. tract endoscopy revealed no gastric or duodenal tumors.
- Abdominal CT scan detected no extracolonic involvement and no desmoid tumors.

Histology

Bioptic polypectomy of 2 lesions was performed during colonoscopy. The first fragment was described as being a hyperplastic adenomatous tubular polyp with minimal dysplasia, and moderate fibrosis with lymphoplasmocytic infiltrate of the chorion. The second fragment turned out to be an adenomatous tubulo-villous polyp with minimal dysplasia.

Surgical treatment

A prophylactic subtotal colectomy and ileoproctostomy with intraoperatory diathermy of the residual polyps seemed to be the ideal procedure for this case. Avoiding to sacrifice the rectum was a satisfactory option because the patient had few rectal polyps and the concern about keeping a near-normal bowel movement pattern. (Figure 3-4)

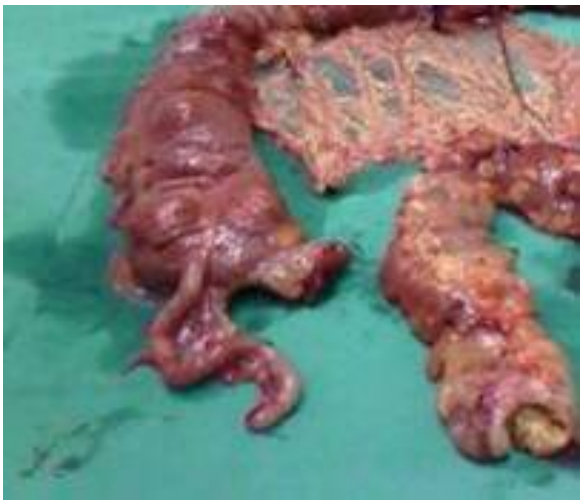
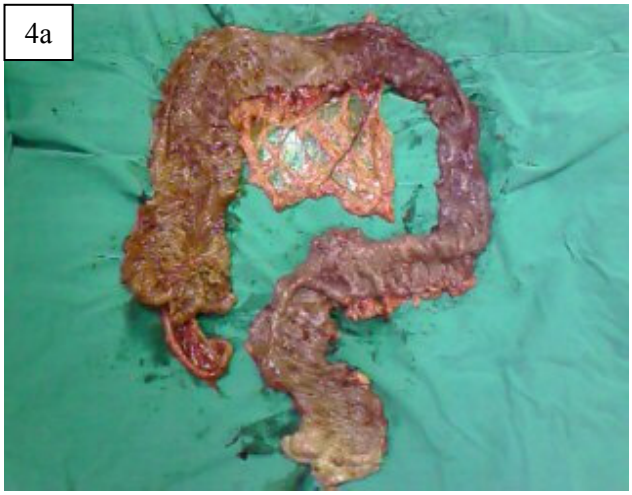


Figure 3 – Colon subtotally resected.



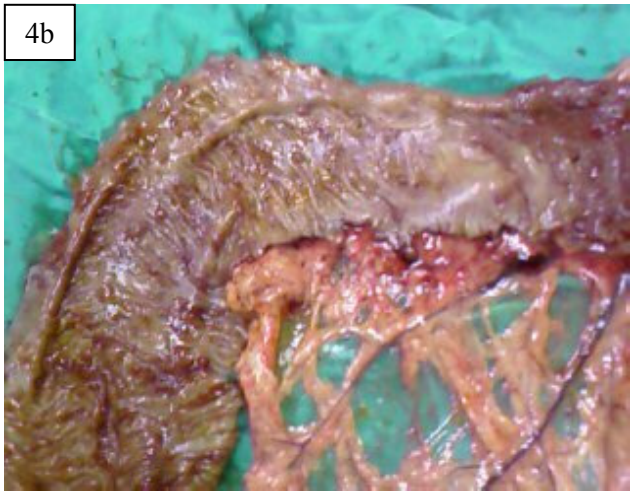


Figure 4a-4b – Resected colon was sectioned longitudinally to reveal multiple adenomatous tubulo-villous polyps involving the entire length of the colon.

Long-term management

1. Complete physical exam every year.
2. Stool blood testing every year.
3. Upper endoscopy at least every 4 years.
4. Flexible sigmoidoscopy every 6 months for monitoring and diathermy of residual and subsequent rectal polyps.
5. Intrarectal administration of 50 mg of indomethacin suppository once or twice daily to control the rectal remnant polyps.

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