FAMILIAL ADENOMATOUS POLYPOSIS: A CASE REPORT AND REVIEW OF THE LITERATURE

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Familial adenomatous polyposis (FAP) is an autosomal dominant condition characterized by diffuse intestinal polyposis, specific gene mutation, and predisposition for developing colon cancer. Left untreated, patients with FAP will develop colorectal carcinoma during early adulthood. Hence, early detection and surgical intervention are of the utmost importance. Colectomy is required and may include an ileal pouch with ileoanal anastomosis, which eliminates the colon and rectal disease while preserving fecal continence and avoidance of a permanent ileostomy.

Advances in the treatment of FAP with associated reduction in mortality from colorectal carcinoma make extracolonic manifestations of the disease more common and life-long surveillance is mandatory. The most life-threatening extracolonic manifestations of FAP are periampullary carcinoma and desmoid tumors. The upper gastrointestinal tract should be monitored endoscopically at the time of diagnosis and assessed regularly thereafter. Duodenal adenomas should be resected so as to avoid the devastating effects of invasive periampullary carcinoma. Additionally, the development of desmoid tumors needs to be monitored (by CT or MRI), so as to avoid the severe complications of local invasion. Further research is indicated in the development of effective screening and treatment for this condition. (*J Natl Med Assoc.* 2001;93: 208–213.)

Key words: polyposis ♦ colon

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited cancer-predisposition syndrome that is causally linked to the adenomatous polyposis coli (APC) gene located on chromosome 5q21. Familial adenomatous polyposis is defined as an inheritable condition in which the large intestine contains multiple adenomatous polyps (typically more than 100).[1] The reported incidence of the disease ranges from 1 in 5,000 to 1 in 17,000 live births annually.[2] Spontaneous germline mutations are common with resultant cases accounting for 20%–30% of patients with FAP.[3] Disease penetrance is nearly 100% by 40 yr of age.[4] Adenomatous polyps may also develop more proximally in the gastrointestinal (GI) tract, most notably in the stomach and second part of the duodenum.

The natural history of FAP includes the development of adenomatous polyps in the late teens to early twenties. Symptoms typically develop by the third decade of life. The most common symptom is bloody rectal drainage; however, complaints of abdominal pain, tenesmus, diarrhea, and obstruction have been noted.[5] Often, the disease may be asymp-

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tomatic in the absence of malignant transformation of a colonic polyp. Left untreated, death usually occurs at a mean age of 42 yr,[5] which is approximately 20 yr earlier than the mean age of death from sporadic colorectal carcinoma.

CASE REPORT

An 18-year-old male previously diagnosed with FAP, presented to our institution for surgical evaluation. The patient initially reported occasional passage of bloody stool along with significant growth retardation at 10 yr of age. These findings, along with a known family history of FAP (the maternal grandfather and maternal uncle with diagnosed FAP), prompted a detailed evaluation. Examination and colonoscopy demonstrated multiple, diffuse polyps supportive of the diagnosis of FAP. Since his initial diagnosis, the patient has had intermittent episodes of hematochezia, shedding of polyps in the stool, and marked failure to thrive. He has had persistent anemia, requiring three transfusions over the last 13 yr. Other family members have been subsequently diagnosed with FAP, including two maternal cousins. The patient's father died of metastatic colon cancer at age 36, although it is not clear whether he had a previous history of gastrointestinal polyposis. A great uncle (paternal) was also diagnosed with colon cancer. The patient's decision to come for surgical evaluation was made only after the patient's weakness, episodes of lightheadedness, and physical limitations in comparison to his peers made even routine daily activities difficult to accomplish.

On physical exam, the patient's general appearance was that of a preadolescent child. His height (62.5 in.) and weight (79 lbs.) were well below the fifth percentile for an 18-year-old male. His abdomen was soft, nontender, nondistended without organomegaly, masses, or ascites. Positive physical findings were limited to the rectal exam, which demonstrated multiple small polyps, several of which prolapsed through the anus.

Serologic laboratory examinations demonstrated serum hemoglobin of 6.2 gm/dL and hematocrit of 20.4%. The platelet count was slightly elevated at 776,000/μL. The serum electrolytes, prothrombin time/partial thromboplastin time, and liver function tests were within normal limits.

The patient underwent a total proctocolectomy with ileoanal anastomosis with a J-pouch and a temporary diverting loop ileostomy. The resected specimen consisted of a 78-cm length of colon and a 14.5-cm excision of rectum. Pathological exam of the colon demonstrated complete mucosal involvement with numerous polyps that ranged in size from small 0.5-cm sessile polyps to 3.5-cm pedunculated polyps (Fig. 1). Microscopically, the polyps displayed focal moderately severe glandular epithelial atypism (Fig. 2). The 93 colonic lymph nodes were free of tumor. The rectum was similarly carpeted with polyps, most of which were pedunculated and ranged in size from 0.3-cm to 1.8-cm diameter. Additionally, a focus of adenocarcinoma in situ was found arising in a rectal adenovillous polyp (Fig. 3). The 10 rectal lymph nodes were free of cancer. The patient recovered uneventfully and was discharged on the fourth postoperative day.

DISCUSSION

The initial clinical description of multiple polyps of the large bowel is attributed to Menzelio who published his data in 1721.[6] The familial nature of multiple colonic polyposis was not recognized until nearly 100 years later when Cripps reported his findings in 1882.[5] The genetic nature of FAP was further elicited in 1925 by Lockhart-Mummery, who suggested the presence of an inherited predisposition that contributed to the development of adenomatous polyps with the potential for malignant change.[7] It was not until a formalized database was developed by Cuthbert Dukes, who organized the screening of relatives of patients with polyposis during the 1930s and created the first register at St. Mark's Hospital in London, that the natural history of FAP was elicited in several generations.

Continued advances occurred in understanding the intestinal and extraintestinal manifestations of this inherited condition. In the 1950s, Gardner and Stephens described a syndrome comprising extracolonic manifestations of polyposis, including osteomas and soft tissue tumors such as lipomas, fibromas, and sebaceous cysts (Gardner's syndrome). Identification of the specific genetic abnormality was discovered serendipitously in 1986 by Herrera and colleagues [8] when they found a deletion in the long arm of chromosome 5 of a patient with multiple colon and rectal polyps. The possibility that the APC gene was localized to 5q was confirmed by Bodmer and associates,[9] and Leppert and coworkers.[10] These authors further recognized that the

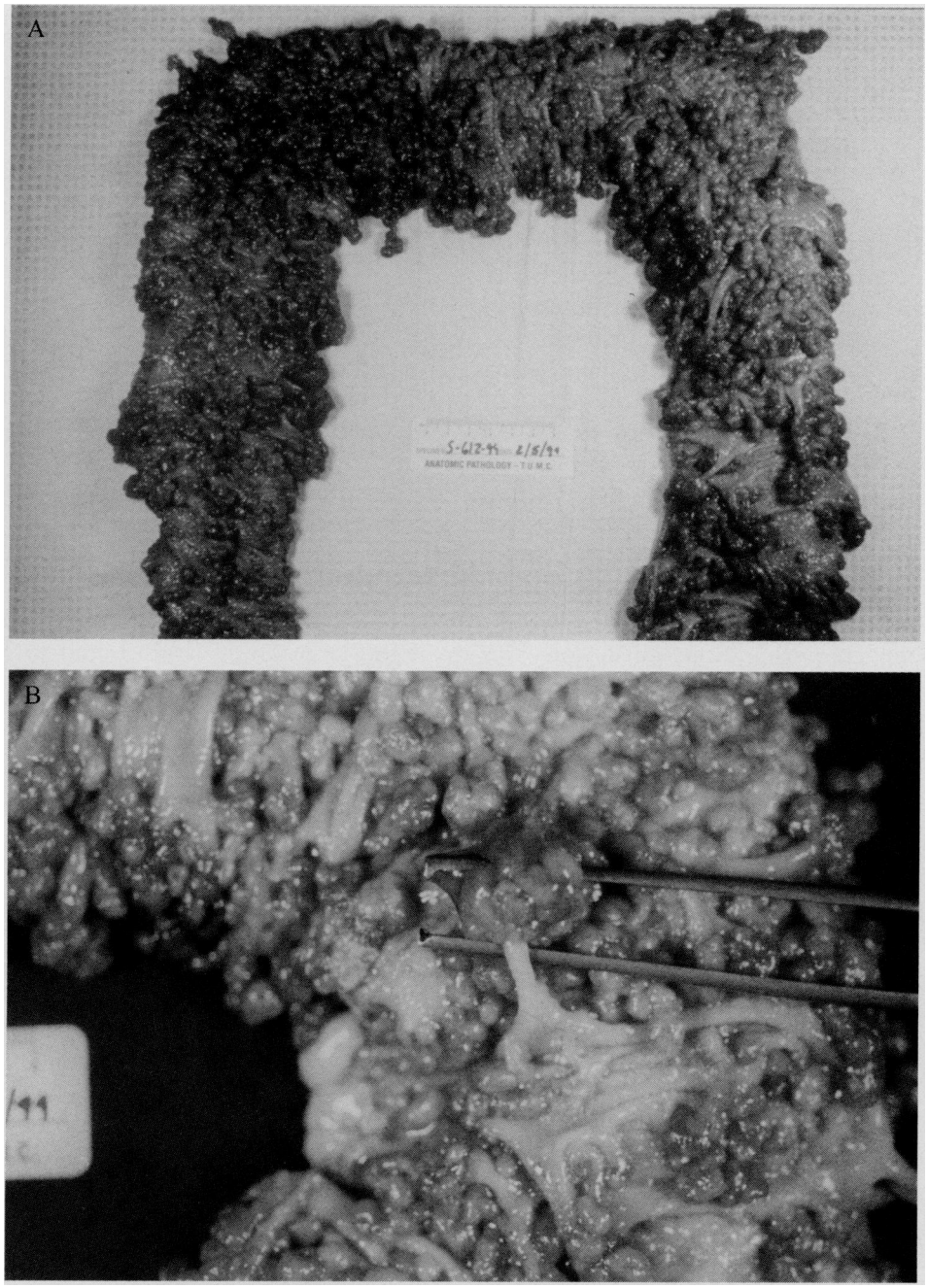

Figure 1. (A and B) Resected colon and rectum with multiple diffuse sessile and pedunculated polyps involving majority of the mucosal surface.

APC gene is a tumor suppressor gene with mutations in the region of 5q21 that lead to hyperproliferative mucosa throughout the gastrointestinal tract and diffuse polyposis.

Diagnosis

Clinical presentation of patients with FAP typically include rectal bleeding or diarrhea, the combination of which usually indicates the development

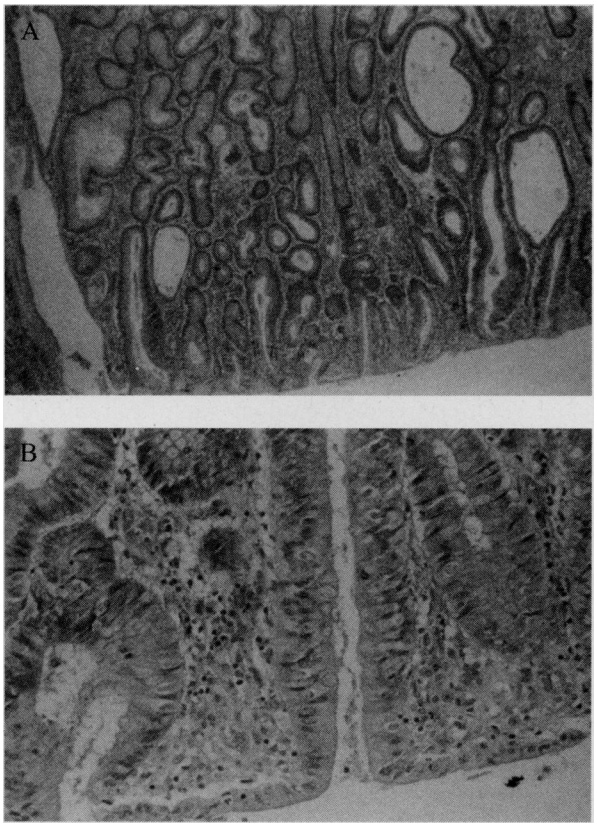

Figure 2. Adenomatous polyp (tubular adenoma) (A) with moderate superficial atypism including hyperchromasia, cellular crowding, nuclear enlargement, and pseudostratification (B).

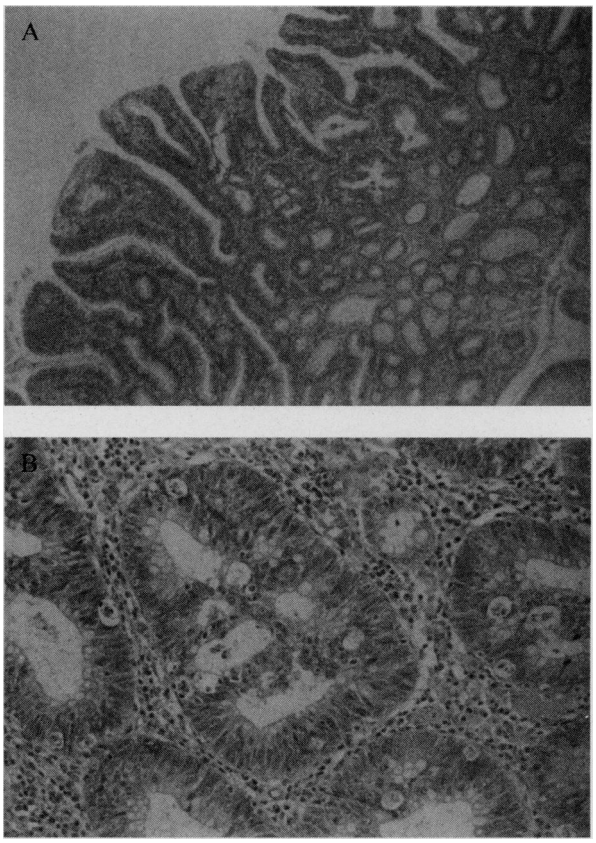

Figure 3. Villous adenoma (A) with changes of severe dysplasia in addition to a focus of cribiform mild dysplasia (B).

of full-blown polyposis. Anemia resulting from blood loss may be present, as is evidenced in our patient. The presence of diarrhea, bleeding, and abdominal cramping is an ominous finding, indicating that these patients may have developed an invasive malignancy.[10] Interestingly, our patient developed symptoms as early as 5 years of age and by age 18 had severe gastrointestinal symptoms. Specific mutations of the APC gene correlate with the degree of colonic polyposis. Although unconfirmed by genetic studies, our patient likely has a mutation between 1250 and 1330, most likely including codon 1309 leading to a more aggressive disease course. Mutations proximal to codon 1249 are associated with sparse polyposis (<1,000 polyps), mutations between codon 1250 and 1330 lead to a profuse phenotype (<5,000 polyps), and mutations distal to codon 1465 again lead to sparse polyposis.[11] Furthermore, a mutation at codon 1309 has been linked to a more aggressive disease course with earlier onset of GI symptoms.[12]

Further diagnostic studies of patients suspected of having FAP include air-contrast barium enema, proctosigmoidoscopy, or colonoscopy. Diagnosis is then confirmed by the histologic findings of adenomatous polyps with a diffuse distribution throughout the large intestines. Esophagogastroduodenoscopy and upper intestinal contrast studies with small bowel follow-through are essential to detect upper GI polyps.

Extracolonic Manifestations

Since Gardner's report of extracolonic manifestations in a family with polyposis, many other clinical features have been recognized. These extracolonic abnormalities are considered to result from a single genetic defect with pleiotropic expression, rather than the result of multiple defects. The modern concept of FAP is that it is a generalized disorder of growth regulation, not a colonic disease

alone. There are many known benign and malignant manifestations of this generalized growth disorder, including osteomas, epidermoid cysts, desmoid tumors, gastroduodenal polyps, small bowel tumors, congenital hypertrophy of the retinal pigment epithelium, hepatobiliary tumors, thyroid tumors, and tumors of the central nervous system. The most worrisome of the extracolonic manifestations of FAP include desmoid tumors and upper GI neoplasia. In a retrospective study at the Cleveland Clinic, Arvantis et al.[13] found the major causes of death in patients with FAP after prophylactic colectomy were periampullary cancers and desmoid tumors.

The realization that gastroduodenal polyps are common in patients with FAP has led to upper GI studies becoming a standard part of the management of these patients. Gastric polyps occur in 34%–100% of patients with FAP, with most being hyperplastic polyps located in the fundus.[14] They do not appear to have malignant potential. Duodenal polyps are more likely to be adenomatous and premalignant and should be ablated by electrocoagulation, snare, or excision.[15]

The risk of periampullary cancer is approximately 10% in patients with FAP.[14] Sagar and Pemberton at the Mayo Clinic[14] advocate annual endoscopic examination with biopsy for patients with duodenal adenomas, thereby allowing early diagnosis and treatment. Asymptomatic patients with negative initial esophagogastroduodenoscopy studies should be re-evaluated every 3–5 years with upper endoscopy including random duodenal biopsies.[16] Malignant transformation should be treated with pancreaticoduodenectomy (Whipple's procedure).

Desmoid tumors occur in approximately 6%–12% of patients with FAP,[16] a much higher frequency than in any other disease. These mesenchymal tumors tend to cause significant morbidity and mortality in patients who have undergone prophylactic colectomy for FAP.[13] These tumors are benign fibrous lesions arising in the musculoaponeurotic soft tissues. They rarely metastasize, but can cause death as a result of local invasion. The majority of desmoids in patients with FAP occur in the small bowel mesentery, although they may also occur in the rectus abdominis muscle and in abdominal incisions. Histopathologic exam demonstrates mature fibroblasts with few nuclei and only occasional mitotic figures.

Desmoids occuring in the small bowel mesentery represent a difficult clinical challenge. Their tendency to recur after surgical resection has led to the recommendation of a non-operative approach in the management of these tumors. Jagelman reported that recurrence of FAP-associated mesenteric desmoids was thus suggesting that surgical resection be reserved for specific complications of desmoids.[17,18]

Treatment

Prophylactic colectomy is required for patients with FAP to avoid the development of invasive colon cancer. Operative management includes removal of all large bowel mucosa that is at risk for malignant transformation while preserving near-normal bowel function and avoiding an ileostomy whenever possible. The operation should additionally preserve normal urinary bladder function and erectile as well as ejaculatory function in males. Options of therapy are: (a) total proctocolectomy with a Brooke ileostomy; (b) subtotal colectomy with ileorectal anastomosis; and (c) restorative proctocolectomy, including the formation of an ileal reservoir and an ileoanal anastomosis.[5]

Proctocolectomy with a Brooke ileostomy has the advantage of being a straightforward procedure with a relatively low postoperative complication rate and very low mortality rate. It is the operation of choice for patients presenting with carcinoma of the lower rectum, for which excision of the anal sphincter is inevitable.[5] The disadvantages of this procedure involve issues associated with a permanent ileostomy. Additionally, creation of a stoma may be a significant deterrent to other family members who require screening and who may be faced with cosmetically undesirable surgery as a prophylactic measure.

Subtotal colectomy with ileorectal anastomosis has been the most popular treatment for FAP and remains an excellent therapeutic approach in select patients. This procedure removes the diseased colon but leaves the rectum in situ. This procedure avoids the need for a permanent ileostomy and reduces the risk of damage to the pelvic nerves. The functional results are variable and largely dependent on the compliance of the residual rectum. The operation is well-suited for patients who desire absolute preservation of the presacral nerve and has the absence of significant rectal polyps, and is willing to undergo regular surveillance of the residual

rectum.[14] The reported risk of developing cancer in the rectal remnant varies from 13%[19] to as high as 59%[20] after 25 years. Factors that may account for the outcome differences are age of the patient at initial operation, length of the retained rectal segment, quality and frequency of sigmoidoscopic follow-up, and cancer in the resected colon.[21]

Restorative proctocolectomy with pouch formation and ileoanal anastomosis is an ideal surgical procedure for disease eradication in patients with FAP. The advantages include complete removal of all the large bowel mucosa, thereby eliminating colonic manifestations of the disease and risk of malignancy. Additionally, adequate bowel function is preserved and a permanent ileostomy is avoided. Bowel movements are generally of acceptable caliber and frequency with very few episodes of urgency, especially at night. Preservation of the sacral plexus during proctectomy maintains erectile and ejaculatory function thus making this procedure especially appealing to younger patients. Visualization of the sacral plexus with complete preservation was performed in our patient using meticulous sharp dissection. This procedure was further indicated in our patient due to the extensive disease involvement of his rectum.

The complications of this procedure include, pouchitis, pelvic sepsis, anastomotic breakdown, and bowel obstruction. Performing a two-stage procedure by creating a temporary diverting loop ileostomy allows time for the anastomosis to heal minimizing anastomotic complications. Additionally, pouchitis is quite rare when restorative proctocolectomy is performed for FAP.[22] Overall, the ileoanal procedure appears to have particularly satisfactory outcome and is the procedure of choice for most patients.

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