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Hypothesis: Extracolonic manifestations have a major effect on the morbidity and mortality of patients with familial adenomatous polyposis following proctocolectomy.

Design: Case review study.

Setting: Colorectal unit, university-affiliated hospital.


Interventions: Ileal pouch–anal anastomosis (n=41), Kock pouch (n=1), end ileostomy (n=6). Two patients underwent total colectomy with an ileorectal anastomosis.

Main Outcome Measures: Clinical follow-up and telephone interview; contact with clinicians following up patients elsewhere.

Results: The patients’ median age at surgery was 33 years. The mean length of follow-up was 74 months. Four patients were lost to follow-up. Extracolonic manifestations were diagnosed in 38 patients (76%). Twelve patients had 14 desmoid tumors: 7 were treated surgically and 7 medically (these patients received celecoxib and tamoxifen citrate therapy). Of the 41 patients who underwent upper gastrointestinal tract endoscopy, 11 developed duodenal and/or ampullary adenomas. Three patients had endoscopic polypectomy and 1 underwent a Whipple operation. Among the 29 patients who underwent pouchoscopy, 5 had pouch adenomas and 3 had adenomas that were found in the rectal stump. Two patients died—one of a huge mesenteric desmoid tumor and the other of an aggressive mesenteric malignant fibrous histiocytoma.

Conclusions: Long-term morbidity and mortality were strongly related to the development of mesenteric tumors and ampullary-duodenal polyps. Early detection of desmoid tumors, duodenal, pouch, and rectal cuff adenomas by periodic computed tomography, gastroduodenoscopy, and pouchoscopy, respectively, may allow control by medical therapy, endoscopy, or limited surgical procedures. In most patients control of desmoid tumors was achieved using a combination of celecoxib and tamoxifen citrate therapy.

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Familial adenomatous polyposis (FAP) is an inherited autosomal dominant disorder that affects 1 to 8 per 10000 persons, both sexes equally, and has been reported in all racial and ethnic groups.1,2 Usually beginning in the subject at puberty, FAP is characterized by the development of hundreds to thousands of adenomatous polyps in the colon and rectum with a tendency to undergo malignant transformation.3 Colorectal cancer was once the main cause of mortality;1 the establishment of national registries, early diagnosis, and prophylactic proctocolectomy have reduced the risk of colorectal adenocarcinoma and changed the pattern of morbidity and mortality. Today, the development of desmoid tumors and of duodenal and ileal pouch adenomas are the focus of special attention and lifelong surveillance. We describe our 15-year experience with patients who had FAP after proctocolectomy to determine the extent to which extracolonic manifestations affect morbidity and mortality.

See Invited Critique at end of article

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METHODS

PATIENTS

All patients with FAP operated on in our department between January 1988 and October 2003 were eligible for inclusion in this study. These patients’ conditions were followed up routinely in the surgical and gastroenterological outpatient clinics. Review of the case notes was supplemented by telephone interview or

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contact with clinicians following up some of these patients elsewhere. The retrieved data included demographics and background diseases, indications for and types of operative interventions, extracolonic manifestations, and further interventions relevant to the disease.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SAS System for Windows, version 8.01 (SAS Institute Inc, Cary, NC).

RESULTS

Fifty patients (25 males and 25 females) with FAP underwent surgery. Their median age at the time of colectomy was 33 years (age range, 13-61 years). The diagnosis was based on endoscopic findings, and an active protein C gene mutation was identified in 31 patients. Twenty-seven patients were derived from 11 families. Forty-eight patients eventually underwent proctocolectomy: 41 (84%) had restoration of continuity with an ileal pouch–anal anastomosis (IPAA), 1 had a Kock pouch, and 6 had an end ileostomy. Six patients underwent total abdominal colectomy with an ileorectal anastomosis (IRA) as the initial procedure: 1 failed conversion to IPAA, 2 were converted to IPAA, and 1 was converted to a Kock pouch. Two patients still have an IRA. Among the patients with IPAA, 22 had a stapled anastomosis and 19 had a handsewn anastomosis. The mean follow-up duration was 74 months (range, 3-288 months). Four patients were lost to follow-up. We report these data about 46 patients.

Eight (16%) had colorectal carcinoma. It was diagnosed before surgery in 3 patients, intraoperatively in 4 patients, and developed in the rectal stump during the follow-up period in 1 patient.

The baseline preoperative extracolonic manifestations of the study patients are given in Table 1. Upper gastrointestinal tract endoscopy was done on 39 patients before surgery. There were no untoward findings in 27 patients after undergoing physical examination. Eleven patients had fundic gland polyps or duodenal adenomas with low-grade dysplasia or both. Preoperative abdominal imaging (computed tomographic scan or ultrasonography) was done in 36 patients and found to have no abnormal findings for any abdominal tumor.

The extracolonic manifestations found at operation and during follow-up are summarized in Table 2. Eight patients were diagnosed as having phenotypic Gardner syndrome (FAP accompanied by osteomas, epidermoid cysts, dental abnormalities, and desmoid tumors) expression and 1 with a variant of Turcot syndrome type 2 (FAP and medulloblastoma). The most common manifestations were osteomas, occurring in 15 patients of whom only 2 were symptomatic. One patient underwent an osteotomy for dental malocclusion, and 1 has hypoacusis due to an osteoma in the external auditory meatus. Forty-one patients (7%) underwent upper gastrointestinal tract endoscopy using a side-viewing duodenoscope. Twenty patients (49%) had polyps of which 65% of these polyps were of the benign fundic gastric type. Fourteen patients (70%) had duodenal polyps of which 1 polyp was periampullary and 4 polyps were located in the papilla (Figure 1). Thirteen patients (65%) had adenomas with low-grade dysplasia: 3 underwent en-

*Endoscopic polypectomy and/or papillectomy.
†Endoscopic resection in 2 patients and surgical polypectomy in 1 patient.
Table 3. Desmoid Tumors

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Presence of Gardner Syndrome</th>
<th>Time of Diagnosis, mo</th>
<th>Interval Since First Operation, mo</th>
<th>Location</th>
<th>Surgical Procedure</th>
<th>Indication</th>
<th>Medical Treatment Received</th>
<th>Status at Last Follow-up Visit</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>At follow-up</td>
<td>16</td>
<td>Retroperitoneum</td>
<td>R nephrostomy</td>
<td>Ureteral, obstruction</td>
<td>Tamoxifen citrate and celecoxib</td>
<td>Regression, nephrostomy</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>At follow-up</td>
<td>34</td>
<td>Mesentery</td>
<td>SB resection, bypass, unresectable</td>
<td>SBO</td>
<td>Tamoxifen and celecoxib</td>
<td>No change</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>At follow-up</td>
<td>8</td>
<td>Mesentery</td>
<td>No</td>
<td></td>
<td>Tamoxifen and sulindac</td>
<td>Progression, dead</td>
<td>Dead</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>At follow-up</td>
<td>9</td>
<td>Mesentery</td>
<td>No</td>
<td></td>
<td>Tamoxifen and celecoxib</td>
<td>Complete regression</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>At follow-up</td>
<td>14</td>
<td>Mesentery</td>
<td>No</td>
<td></td>
<td>Tamoxifen and celecoxib</td>
<td>No change</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>At follow-up</td>
<td>40</td>
<td>Mesentery</td>
<td>No</td>
<td></td>
<td>Tamoxifen and celecoxib</td>
<td>Regression</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>At follow-up</td>
<td>26</td>
<td>Mesentery</td>
<td>Partial resection and SB resection</td>
<td>SBO</td>
<td>Tamoxifen and celecoxib</td>
<td>Regression</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>At follow-up</td>
<td>50</td>
<td>Abdominal wall</td>
<td>Resection, mesh repair</td>
<td>Cosmetic</td>
<td>Tamoxifen and celecoxib</td>
<td>No desmoid tumor</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>No</td>
<td>Operation 1</td>
<td>0</td>
<td>Mesentery</td>
<td>Resection and SB resection, incidental bleeding</td>
<td>Small incidental</td>
<td>Tamoxifen and celecoxib</td>
<td>No desmoid tumor</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>Operation 2</td>
<td>162</td>
<td>Mesentery</td>
<td>Resection and SB resection</td>
<td>Bleeding</td>
<td>Tamoxifen and celecoxib</td>
<td>No desmoid tumor</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>No</td>
<td>Operation 2</td>
<td>167</td>
<td>Mesentery</td>
<td>No</td>
<td></td>
<td>Tamoxifen and celecoxib</td>
<td>No change</td>
<td>Alive</td>
</tr>
<tr>
<td>12</td>
<td>No†</td>
<td>At follow-up</td>
<td>16</td>
<td>Mesentery</td>
<td>No</td>
<td></td>
<td>Tamoxifen and celecoxib</td>
<td>No change</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Abbreviations: SB, small-bowel; SBO, small-bowel obstruction.

*The following doses were given: tamoxifen citrate, 120 mg/d, and celecoxib, 800 mg/d.
†This patient had Turcot syndrome type 2.

Most desmoid tumors were diagnosed during the follow-up period; the median interval from the first laparotomy was 26 months (range, 8-234 months). One patient was operated on 15 years after having an IRA because of numerous rectal polyps. During surgery, a mesenteric desmoid was found that precluded the performance of an IPAA procedure, and the patient underwent proctectomy and ileostomy. One patient was diagnosed as having pinealoblastoma, papillary thyroid carcinoma, and multiple colonic polyps and was considered as probably having a variant of Turcot syndrome type 2. Multiple mesenteric desmoid tumors developed in this patient 16 months after IPAA. The surviving 11 patients are being treated with a combination of tamoxifen citrate, 120 mg/d, and the cyclooxygenase 2 inhibitor celecoxib, 800 mg/d, and the disease is stable or in regression in all, including 2 patients who were operated on for small-bowel obstruction, 10 and 6 years ago, and 1 patient with hydronephrosis that was relieved by nephrostomy (Figure 2). In 1 patient, the tumor decreased in size during 4 years of follow-up. There has been no tumor recurrence in the patients who were treated in an adjuvant setup after excision.

Two patients died. One patient who had been lost to follow-up was admitted to the hospital 5½ years after colectomy and ileorectal anastomosis because of an acute abdomen and underwent emergent surgery. This patient had small-bowel perforation due to an aggressive mesenteric tumor that was found on histologic study to
be a malignant fibrous histiocytoma. The patient died a few months later owing to intra-abdominal tumor spread. The other patient had a huge intra-abdominal desmoid tumor and died 9 months after IPAA. The tumor was already identified at operation: it was 1 cm in diameter, situated in the small-bowel mesentery, grew perniciously to huge extensions (>30 cm), and caused deep vein thrombosis and a fatal pulmonary embolism.

**COMMENT**

For many years, the main cause of mortality in patients with FAP was colorectal cancer. In 1925, Lockhart-Mummery demonstrated that prophylactic examination of family members at risk and colectomy in affected individuals reduced the frequency of colorectal cancer, leading to the founding of the St Mark’s Hospital Polyposis Registry as the first polyposis registry in the world. In 1985, the Leeds Castle Polyposis Group was established as an international polyposis research forum. Polyposis registries have since been established in many countries, and this brought about a decrease in colorectal cancer prevalence and overall improvement in prognosis. It is well recognized that patients afflicted with the syndrome must undergo prophylactic surgery to extirpate the large bowel, which carries a 100% risk of developing cancer.

There is some debate in the literature on IRA vs IPAA in a selected group of patients, with proponents of the IRA citing the relatively low morbidity, better quality of life, and ease of surveillance as benefits of the technique. Studies that evaluated these 2 techniques in patients with FAP, however, have failed to show a greater morbidity and poorer functional outcome for IPAA compared with IRA. Some studies showed that IRA is associated with substantial mortality due to rectal cancer, regardless of the length of follow-up.

The mortality pattern of patients with polyposis has changed substantially, and the most frequent causes of death in patients whose conditions were detected through screening are desmoid tumors and duodenal cancer. In countries with regular surveillance, such as in the Scandinavian region, cases of colorectal cancer in patients with polyposis have become rare and occur almost entirely in probands who represent a new mutation. We have had no mortality from colorectal cancer in our current series. There is 1 patient who had a recurrence 37 months after resection of stage III carcinoma.

Among the great variety of extracolonic manifestations of FAP, there are 3 manifestations that require special attention and lifelong surveillance. The first appears in the form of adenomatous polyps of the stomach, duodenum, and small bowel and occurs in almost 100% of patients with FAP. Gastric cystic fundic gland polyps are common but rarely associated with malignancy. The second portion of the duodenum, especially the periampullary area, is the one prone to adenomatous transformation. Three percent to 8% of patients eventually have duodenal or periampullary cancer, a risk that increases if there is a family history of such occurrence. A 10-year prospective study by Groves et al reported that 6 of 114 patients with FAP developed duodenal adenocarcinoma. In our series, 10 (20%) of 50 patients had duodenal polyps. One patient had pancreatoduodenectomy due to adenoma with high-grade dysplasia. Adenomas of the gastric antrum and other portions of the small bowel also occur but with lesser frequency.

The second manifestation is the development of adenomas within the ileal pouch several years after restorative proctocolectomy. The reported incidence ranges between 20% and 62% and depends on duration of follow-up. Parc et al found that the risk of developing adenomas at 5, 10, and 15 years was 7%, 35%, and 75%, respectively. The incidence was about 5 (17%) in our group of 29 patients, a figure that correlates well with the aforementioned data. The risk of cancer development in such adenomas has not been established. Patients with FAP are also at risk of developing adenomas and cancer in the anal transitional zone. In our series, 9 (18%) patients in the stapled IPAA group developed adenomas in the retained rectal mucosa. No cancer was found.

The third and major cause of morbidity and mortality in patients with FAP is abdominal desmoid tumors, the incidence of which ranges between 7% and 17% during a lifetime. Our incidence of 26% is higher than the reported one. Desmoid tumors are histologically benign and do not metastasize, but they do tend to invade locally. Mesenteric desmoid tumors may cause small-bowel obstruction or ischemia, hydronephrosis, or the formation of fistulas. It has long been recognized that surgical trauma triggers the development of desmoid tumors. In the reported cases in our series, all tumors but 2 (82%) of the tumors appeared after surgery. Heiskanen and Järvinen analyzed 202 patients with FAP and found that 83% developed desmoid tumors postoperatively. Together these findings support the contention that the approach to these benign, but aggressive, tumors should be conservative. Surgery may be hazardous by involving major small-bowel resection, and the recurrence rate after debulking is high, ranging between 75% and 85%. Therefore, surgery is reserved for life-threatening complications.

Radiotherapy and chemotherapy are associated with high complication rates, and their efficacy is questionable. Although controversial, chemoprevention has been shown in some studies to be effective in reducing the num-
ber of adenomatous polyps, mainly in the colon.27-29 The treatment with sulindac and tamoxifen has been documented to restrain the growth of desmoid tumors, and even cases of regression have been reported.30 Control in larger series with longer follow-up.26

An important issue is the choice of a prophylactic colec-rectal procedure in light of possible desmoid tumor for-ation. After IRA and IPAA, the risk has been estimated to be 12% and 17%, respectively.25 Most centers have preferred IPAA to IRA over the past decade. When a desmoid tumor is found at the time of the first laparotomy, IPAA should be seriously considered, if technically feasible. The reason for this is that up to 34% of patients may require further surgery after colecotomy and IRA because of uncontrollable rectal polyps or cancer,26 and conversion may not be feasible because of the presence of a mesenteric desmoid tumor, as had occurred in one of our patients. The genetic susceptibility, family history of desmoid tumors, and early age at diagnosis should be considered when the choice of operation is made.31

CONCLUSIONS

The 2 main causes of long-term morbidity and mortal-ity are adenomas in the upper gastrointestinal tract, pouch, and anorectal mucosa and desmoid disease. Long-term surveillance by gastroduodenoscopy and pouchoscopy in all patients with FAP are mandatory and computed to-mographic scanning in high-risk patients should be considered. Early detection may allow control of this life-threatening condition by means of medical therapy and an endoscopic or limited surgical procedure. Further re-search should be aimed at the prevention and treatment of these growths to improve survival. A prospective study on the role of chemopreventive treatment in patients prone to develop desmoid tumors is warranted.

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REFERENCES

The genetics of FAP can be a nightmare. An enduring concern in the treatment of FAP is the course of the disease after colectomy; its rarity and its clinical heterogeneity limit our understanding of extracolonic neoplastic manifestations, especially if these develop at a relatively advanced age. Tulchinsky et al report their experience with several extraintestinal complications of FAP; they have also highlighted several factors that influence their choice of prophylactic surgery, including the risk of rectal tumor development and desmoid tumors. Further comment is merited about the correlation between the phenotype: the clinical behavior of FAP, and the mutation in the adenomatous polyposis coli (APC) gene on chromosome 5q21; such a mutation is detectable in about 80% of the patients with FAP. Although its testing is increasingly more accessible, there is a compelling need for genetic counseling.

The molecular pathophysiology of phenotype-genotype correlations in FAP is poorly understood but seems to stem from the specific protein domain inactivation associated with different mutations within this gene. Other exogenous and endogenous factors, including modifier genes, contribute to the clinical heterogeneity of FAP.

Our experience indicates a greater risk of dysplastic gastric fundic gland polyps and duodenal adenomata in pediatric patients with APC mutations between codons 1225 and 1694. The risk of rectal stump cancer complicating IRA has been similarly characterized; Wu et al described severe polyposis in patients harboring APC mutations at codons 1309 or 1328. They stressed that the prognosis for retaining the colon in these patients is poor. Bertario et al addressed the question of rectal stump cancer in patients with FAP treated with IRA vis-a-vis APC mutations; they described a significantly greater rectal polyp burden and higher rectal stump cancer risk in patients harboring mutations between codons 1250 and 1464 compared with individuals with mutations upstream or downstream of this segment of the APC gene. The same group has further characterized a markedly increased risk of developing desmoid disease in patients with FAP harboring APC mutations upstream of codon 1444 (odds ratio, 11.6≤codon 1444 compared with >codon 1444).

Future studies will have to address the effect of a more comprehensive approach to treatment of FAP, including APC and human homolog of mutY (MYH) gene mutation analysis, to anticipate the course of the disease. Novel techniques in improving survival include laparoscopic surgery for colectomy, and the effect of chemopreventive agents.

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