Epidemiologic Characteristics of the Flat Adenoma of Muto

A Prospective Study

S. J. Lanspa, M.D., J. Rouse, M.D., T. Smyrk, M.D., P. Watson, Ph.D., J. X. Jenkins, M.D., H. T. Lynch, M.D.

From St. Joseph Hospital at Creighton University Medical Center, Omaha, Nebraska

The flat adenoma is an endoscopically visible lesion that histologically consists of adenomatous change near the luminal surface of colonic tubules. We have described three families with hereditary colon cancer with later age of onset than familial adenomatous polyposis (FAP) and with multiple proximal colonic flat adenomas. These families have been linked to the FAP locus on chromosome 5. Our aim was to determine whether the flat adenoma is pathognomonic of this hereditary flat adenoma syndrome (HFAS) or merely an atypical or early tubular adenoma with occurrence in patients other than those from colon cancer-prone families. Methods: We prospectively examined a population referred for colonoscopy within a one-year period. During colonoscopy, flat adenomas were specifically sought and all lesions were removed endoscopically and evaluated histologically. Members of known hereditary colon cancer families were excluded. Results: One hundred forty-eight patients underwent colonoscopy (64 men and 84 women). Median age was 61 years. Fifty-seven patients had 157 polyps. One hundred thirty-six polyps were reviewed histologically. Thirty-five (23.6 percent) of the referred patients had adenomas, of whom twelve patients had only flat adenomas while six had both flat and other adenomas (18 = 12 percent of 148). The associations between flat adenoma occurrence and various predictors (sex, race, prior colonic neoplasms, family history of cancer, synchronous adenomas) were similar to those seen with other adenomas. Flat adenomas were found in nearly equal proportions of patients under or over age 61 years (11 percent and 13 percent, respectively). Other adenomas were significantly more common in the older group (6 percent *vs.* 25 percent; $P < 0.002$ by Fisher's exact test). Conclusion: In a referral practice, the flat adenoma has the same prevalence and associated risk factors as other adenomas, except for younger age of onset. Our data suggest that the flat adenoma represents an early stage of adenoma development that is manifested in a subset of patients from the general population and that, as an isolated event, does not provide a marker for a hereditary colon cancer-prone syndrome. [Key words: Adenoma; Polyp]

Lanspa SJ, Rouse J, Smyrk T, Watson P, Jenkins JX, Lynch HT. Epidemiologic characteristics of the flat adenoma of Muto: a prospective study. Dis Colon Rectum 1992;35: 543–546.

Supported in part by NCI Grant 5 ROI CA-42705.

Address reprint requests to Dr. Lanspa: Associate Professor of Medicine, Division of Gastroenterology, Creighton University Medical Center, 601 N. 30th, Omaha, Nebraska 68131.

Muto and colleagues[1] described a colonic mucosal lesion that was small and flat and that microscopically was a tubular adenoma with adenomatous changes concentrated in the luminal surface of the mucosa. They termed this the flat adenoma. They did not ascertain family histories on these patients. Muto *et al.*'s article described an unusually high prevalence (42 percent) of high-grade dysplasia. During colonoscopic surveillance studies of high-risk colon cancer families, we recognized a family in which many members had multiple adenomas, the majority of which were located in the right colon.[2,3] Many of these adenomas had the gross and microscopic features of flat adenomas. This large cancer-prone kindred showed an autosomal dominant inheritance pattern for the transmission of colon cancer and frequent occurrences of flat adenomas. We have since described two additional families showing a strikingly similar autosomal dominantly inherited flat adenoma and colorectal cancer phenotype[4] and have termed this the hereditary flat adenoma syndrome (HFAS). We wish to determine whether the flat adenoma provides a marker for a hereditary colon cancer-prone syndrome or is merely an atypical or early tubular adenoma.

METHODS

We prospectively examined a population referred for colonoscopy to seek flat adenomas and ordinary tubular adenomas in patients who are not at high risk for hereditary colon cancer. We compared these polyp variants in terms of epidemiologic risk factors, age distribution, and frequency of high-grade dysplasia. Patients were from a clinical gastroenterology practice and had been referred to Creighton University Medical Center from September 1989 to September 1990. Colonoscopy was performed in a routine fashion using intrave-

nous light sedation. A video colonoscope was used for all patients. Unselected patients were referred for evaluation of guaiac-positive stools, iron deficiency anemia, prior history of colonic neoplasms, abnormal barium enema, inflammatory bowel disease or chronic diarrhea, and polyps noted on screening flexible sigmoidoscopy and for evaluation prior to esophageal resection with colonic interposition. Members of families known to be affected with hereditary colon cancer (Lynch syndrome, familial adenomatous polyposis [FAP], or HFAS) were excluded. For all the colonoscopy patients, family history of cancer at all anatomic sites inclusive of first- and second-degree relatives was recorded.

RESULTS

One hundred forty-eight patients underwent colonoscopy. Median age was 61 years, with a range of 20 to 93 years. There were 64 men and 84 women. The majority of patients were Caucasian Americans, 15 patients were African Americans, one patient was Asian American, two patients were Hispanic, and one patient was a native of India. Thirty-five patients had prior personal history of colonic adenomas or colorectal cancer (Fig. 1). Seventeen patients had a family history of colon cancer (14 with a first-degree relative affected and six with a second-degree relative affected). Two patients had two first-degree relatives affected with colon cancer. Thirty-seven patients had family history of other anatomic sites of malignancy or first- or second-degree relatives with cancer, anatomic site unknown. Extended pedigrees were not obtained on these patients.

Thirty-five patients had a prior history of colonic neoplasm. Fifty-five patients had polyps noted at colonoscopy. One patient had cecal cancer with no polyps (Fig. 1).

The colonoscope was passed into the cecum in 99.3 percent of cases. There were no complications of colonoscopy or polypectomy. One hundred fifty-seven polyps were noted on colonoscopy. One hundred thirty-six specimens were re-examined for microscopic characteristics of flat adenoma. Polyps were interpreted by two reviewing pathologists (J.R., T.S.) unaware of the patient's background or endoscopic appearance of the lesion and were classified as flat adenomas if the adenomatous changes in the tubules on multiple sections were confined to the luminal aspect of the crypts.

Sixty-six of the polyps were adenomas. Six were lymphoid aggregates. The remainder were hyperplastic or normal tissue. Twelve patients had multiple adenomas. Three adenomas had focal high-grade dysplasia: one tubular adenoma (15 mm), one villous adenoma (12 mm), and one tubulovillous adenoma (25 mm). Dysplasia was not seen in any of the flat adenomas. Overall, 18 patients (12 percent) had flat adenomas. The maximum number of flat adenomas found in any one patient was three.

The distribution of flat adenomas differed significantly from that of other adenomas ($P < 0.01$). The highest proportion of flat adenomas was found in the transverse and sigmoid colon, whereas the highest proportion of other adenomas was seen in the rectum (Fig. 2).

We evaluated differences in prevalence rates of

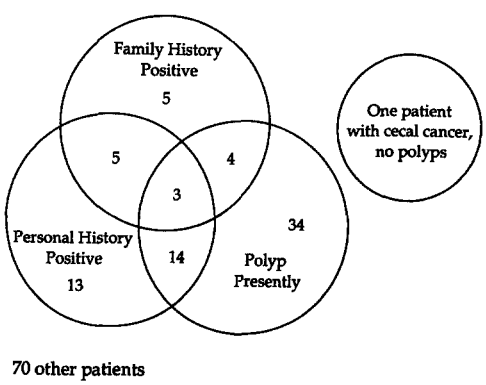

Figure 1. Patients studied. Distribution of colon neoplasia in regard to cancer history.

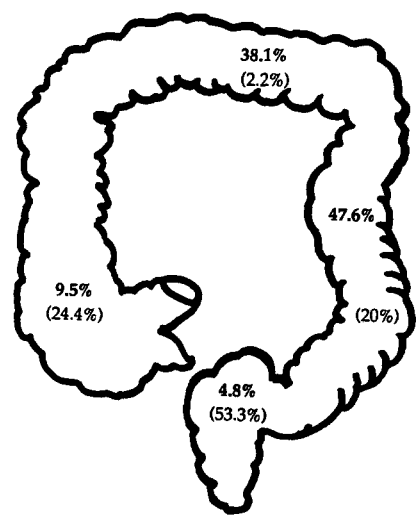

Figure 2. Distribution of colorectal adenomas. The distribution of flat adenomas differed significantly ($P < 0.01$) from that of the other adenomas (shown in parentheses).

flat adenomas among sex, prior history of colorectal neoplasia, family history of colorectal neoplasia, and race (Fig. 3). For these patient parameters, the prevalance rates of flat adenomas were similar to those of other adenomas. Flat adenomas were found in nearly equal proportions among patients under or over age 61 years (11 percent and 13 percent, respectively). Other adenomas were significantly more common in the older group (6 percent *vs.* 25 percent; $P < 0.002$ by Fisher's exact test) (Fig. 3).

DISCUSSION

HFAS is an autosomal dominantly inherited disorder which predisposes to a predominance of proximal colorectal cancer onset (mean age of onset, 55 years) in concert with flat adenomas. It differs from FAP in its later age of onset and general absence of florid polyposis with concentration of adenomas in the cecum and ascending colon.

The present study suggests that flat adenomas are not at all uncommon in referral practice patients when specifically sought (12 percent prevalence). The significance of these subtle lesions had not been known until Muto's "discovery." He suggests that they can be missed on barium enema.

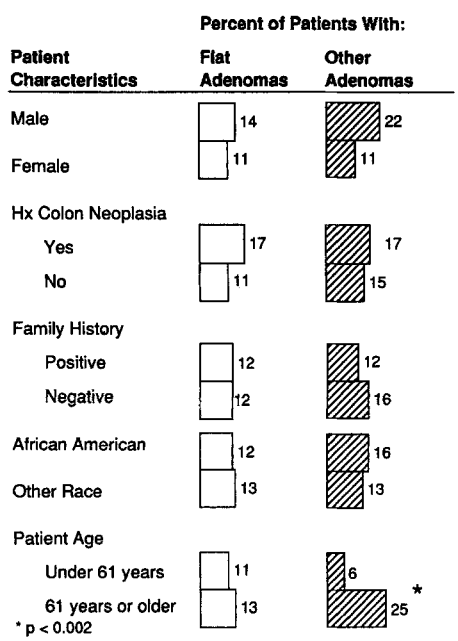

Figure 3. Predictors of colon neoplasia. Prevalence rates of flat adenomas were similar to those of other adenomas among all patient parameters studied except age. While flat adenomas were prevalent in nearly equal rates among patients older or younger than 61 years, other adenomas were significantly more common in the older age group ($P < 0.002$ by Fisher's exact test).

Adachi *et al.*[5] have stressed that these lesions may be missed at colonoscopy. Our experience is that they are best seen with video colonoscope. The difficulty of identifying these lesions can be inferred by the fact that, during a search for flat adenomas, approximately half of the lesions removed were small hyperplastic polyps or normal tissue. Alternatively, these lesions may also have been overlooked in the past if histologic reports listed them as small adenomas without special reference to the luminal distribution of the adenomas' changes.

The difference in distribution between flat adenomas and other adenomas remains unexplained. Our distribution seems similar to that reported by Wolber and Owen.[6] Perhaps differences in anatomic structure of different colonic segments lead to different find rates during colonoscopy.

In Muto *et al.*'s evaluation of the flat adenoma in Japan, these lesions had a high incidence (42 percent) of dysplasia.[1] None of the flat adenomas in our study had high-grade dysplasia (stratification of nuclei and numerous mitotic figures through the full thickness of crypt epithelium with loss of nuclear polarity, marked nuclear atypia, and complete absence of cytoplasmic mucinous differentiation).[6]

Wolber and Owen[6] found an incidence of flat adenomas similar to ours but also noted frequent high-grade dysplasia. Ours is the only prospective colonoscopic series. It seems unlikely that 40 percent of these common adenomas have high-grade dysplasia. Perhaps the presence of high-grade dysplasia somehow leads to a sampling bias. For instance, we do not frequently find the central depression described by others. Flow cytometry may help to standardize subjective findings of high-grade dysplasia among pathologists from different centers.

We have noted flat adenomas in two cases of FAP from two different families. Both patients had florid polyposis carpeting the colon. These patients had postponed colon resection into middle age, and thus the resected colon showed full phenotypic expression with microadenomas, grossly visible adenomas, and adenocarcinomas of the colon. Pathologic study of these resected specimens showed flat adenomas as well. We differentiate these lesions from microadenomas in that they can be seen at endoscopy or by the pathologist at gross inspection. Microscopic adenomas are not visually detectable. The presence of many colonic flat ad-

enomas in patients with FAP further suggests that the flat adenoma is a developmental stage in the life of an adenomatous polyp. We have also seen a flat adenoma in a patient with chronic ulcerative colitis.

In a referral practice, the flat adenoma has a prevalence and associated risk factors similar to those of classic tubular adenomas, except for a younger age of onset. It likely represents an early stage of adenoma development, and its presence alone does not identify a genetic syndrome.

Diagnosis of HFAS, pending discovery of a different biomarker, will require evaluation of the family history with attention to number and distribution of adenomas throughout the colon.

REFERENCES

1. Muto T, Kamiya J, Sawada T, *et al.* Small "flat adenomas" of the large bowel with special reference to its clinical pathologic features. Dis Colon Rectum 1985;28:847–51.
2. Lanspa SJ, Lynch H, Smyrk T, *et al.* Multiple proximal adenomas with atypical features in hereditary colon cancer: a new syndrome? Gastroenterology 1988; 94:A250.
3. Lynch HT, Smyrk T, Lanspa SJ, *et al.* Flat adenomas in a colon cancer-prone kindred. J Natl Cancer Inst 1988;80:278–82.
4. Lynch HT, Smyrk TC, Lanspa SJ, *et al.* Phenotypic variation in colorectal adenoma/cancer expression in two families: hereditary flat adenoma syndrome. Cancer 1990;66:909–15.
5. Adachi M, Muto T, Morioka Y, Ikenaga T, Hara M. Flat adenoma and flat mucosal carcinoma (IIB Type)—A new precursor of colorectal carcinoma? Report of two cases. Dis Colon Rectum 1988;31: 236–43.
6. Wolber RA, Owen DA. Flat adenomas of the colon. Hum Pathol 1991;22:70–4.