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Clinical Characteristics of Multiple Colorectal Adenoma Patients without Germline *APC* or *MYH* Mutations

Alan H. Tieu, MD[1], **Daniel Edelstein, MS**[1], **Jennifer Axilbund, MS**[2], **Katharine E. Romans, MS**[2], **Lodewijk A. Brosens, MD, PhD**[3,4], **Elizabeth Wiley, MS**[2], **Linda Hylind, BS, RN**[1], and **Francis M. Giardiello, MD**[1,2,3]

[1]Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland [2]Department of Oncology Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland [3]Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland [4]Department of Pathology, University Medical Center Utrecht, The Netherlands

Abstract

Background—Patients with multiple colorectal adenomas (MCRA) without genetic cause are increasingly being diagnosed. The characteristics and natural history of this condition are not well studied.

Method—Twenty seven patients with MCRA, with cumulatively 10–99 colorectal adenomas and without deleterious mutations of *APC* or *MYH* genes, were investigated. Results of colonoscopies with mean follow-up of 4.9 years (range 0–27) were evaluated. Findings from esophagogastroduodenoscopy (EGD) and extracolonic manifestations were assessed.

Results—The mean age at polyp diagnosis and MCRA diagnosis was 47.8 ± 13.1 years (range 21–72) and 50.4 ± 14.6 years (range 21–72), respectively. In 22% of patients another family member had MCRA. At first colonoscopy, the mean number of adenomas was 35.0 ± 35.9 (range 0–99). Serrated polyps were rare. EGD revealed 47% of patients had upper tract neoplasia. Patients with upper tract findings were diagnosed with MCRA at significantly younger mean age than those without findings, $p<0.05$. Eighteen patients (67%) underwent colectomy with mean time from diagnosis of MCRA of 3.1 ± 1.3 years. After surgery, surveyed patients developed recurrent adenomas in retained colorectum. Nine patients (33%) had extracolonic cancers.

Conclusions—MCRA patients have a similar clinicopathological phenotype to known syndromes of attenuated adenomatous polyposis and the majority have need for colectomy. The

Correspondence to: Francis M. Giardiello, M.D., The Johns Hopkins Hospital, 1830 East Monument Street, Room 431, Baltimore, MD 21205, Tel: 410-955-2635; Fax: 410-614-8337; fgiardi@jhmi.edu.

Author Involvement:
Tieu- A. B. C. D E. F. G. H., Edelstein - A. B. C. D E. F. G. H., Axilbund - C. D. G. H., Romans - C. D. G. H., Brosens- A. B. C. D E. F. G. H. ,Wiley – D. G. H., Hylind - C. D. G. H., Giardiello - A. B. C. D E. F. G. H.
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Conflicts of Interest
All authors have no conflicts of interest to declare.

management of MCRA patients and families should parallel that of attenuated FAP and *MUTYH*-associated polyposis (MAP) including surveillance of the upper tract.

Keywords

Multiple colorectal adenomas; colorectal cancer; clinical history

INTRODUCTION

Colorectal cancer (CRC) is an important global health concern and the second leading cause of cancer death in United States and Western Europe (1). While most cases of colorectal cancer are sporadic events, inherited factors play a role in some tumors, with an estimated 5% attributed to specific deleterious gene mutations (2). Patients presenting with multiple colorectal adenomatous polyps from known syndromes including attenuated and classic familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis (MAP) have a high lifetime risk for colorectal cancer (CRC).

Familial adenomatous polyposis (FAP) is an autosomal dominantly inherited disease, associated with germline mutations in the *APC* gene. Classic FAP is characterized by the development of hundreds to thousands of adenomatous polyps in the colon and rectum, usually during teenage years, which if not treated will progress to colorectal cancer (3). Attenuated FAP (AFAP) patients present with fewer adenomas at older age with similar high risk of colorectal cancer (4). Approximately 80–93% of individuals with classic FAP and 30% with AFAP have a detectable *APC* gene mutation (5). *MUTYH*-associated polyposis (MAP) is a syndrome characterized by multiple adenomatous polyps and an autosomal-recessive mode of inheritance caused by bi-allelic germline mutations in the base-excision repair gene *MUTYH* (6).

Patients presenting with multiple colorectal adenomas (MCRA) with absence of a germline mutation for AFAP or MAP are being increasingly identified (7). Therefore, the present study evaluates the clinical characteristics of patients with MCRA, defined as patients developing cumulatively 10–99 colorectal adenomas, but without deleterious germline *APC* or *MYH/MUTYH* mutations.

MATERIALS AND METHODS

Study population

Patients with multiple colorectal adenomas (MCRA) enrolled in the Johns Hopkins Hereditary Colorectal Cancer Registry between July 1st 2000 and June 1st 2013 were included in the study. These patients self-enrolled in the Registry either without physician referral or were asked to enroll by a physician who had seen the patient in consultation. All patients were probands and had 10–99 colorectal adenomas at the time of enrollment. Informed written consent for genetic diagnosis was obtained from all patients. MCRA patients were defined as those with (1) cumulatively 10 to 99 colorectal adenomas; and (2) absence of deleterious *APC* and *MYH/MUTYH* mutations by germline testing. This study

was approved by the Johns Hopkins Joint Committee on Clinical Investigation (institutional review board).

Study design

Data was collected on each patient from medical records including colonoscopy, esophagogastroduodenoscopy (EGD) and histopathology reports. Abstracted information included, sex; age; date of colonoscopy; age at each colonoscopy; number of colonoscopies; number, type, and location of colorectal neoplasia; date and findings on EGD; family history of CRC; family history of MCRA; and date and type of surgery. The histopathology of all polyps noted at colonoscopy was verified by histologic review except in patients that had too numerous polyps for endoscopic removal. In these cases the polyp histology was assumed by sampling and was later pathologically confirmed in the colectomy specimen. These patients were not part of a surveillance protocol, and consequently, the interval of surveillance was determined by the judgement of the treating gastroenterologist. Extracolonic characteristics and cancers were recorded. The mean average increase in polyp number per year was calculated. *APC* gene testing was done by full sequencing and comprehensive large segment rearrangements by Southern blot. Full sequence analysis identified mutations in all 15 exons and approximately 440 adjacent non-coding base pairs of *APC*. Southern blot analysis identified duplications and deletions involving one or more exons of *APC*. Promoter and splice site regions of *APC* were not evaluated. *MYH* gene testing was done by full sequencing analysis which included the two most common *MYH* mutations in individuals of European ancestry, Y165C and G382D. Patients enrolled earlier in the study, who initially were evaluated for only the two common *MYH* mutations described above, were retested by full sequence analysis.

Statistical Analysis

Mean, standard deviation, median and range were reported where appropriate. Statistical analysis was conducted using the Fisher exact test and student t-tests. Statistical significance was defined as a p value <0.05. The statistical analyses were performed using the statistical software STATA V.11.

RESULTS

In total, 27 patients (19 males/8 females) had multiple colorectal adenomas (MCRA). The mean ± SD age at polyp diagnosis (when colorectal adenomas were first identified) and MCRA diagnosis was 47.8 ± 13.1 and 50.0 ± 14.6 years, respectively. In 6 of 27 pedigrees (22%) another family member had MCRA.

These patients underwent a total of 93 colonoscopies (Table 1). The indications for the first colonoscopy were CRC screening in 16 patients (60%), gastrointestinal bleeding in 3 (11%), family history of CRC in 2 (7.4%), abdominal pain in 2 (7.4%), positive hemoccult in 1 (3.7%), upper gastrointestinal polyps in 1 (3.7%), and change in bowel habits in 1 (3.7%). The mean ± SD age at first colonoscopy was 47.7 ± 13.1 years and at last colonoscopy was 52.6 ± 12.2 years. The mean colonoscopic follow-up was 4.9 years (range 0–27) and the mean interval between colonoscopy in this patient group was 1.1 year (range 0–8 years).

The mean cumulative number and type of colorectal polyps is shown in Table 2. At first colonoscopy, the mean number of adenomas was 35.0 ± 35.9 (range 0–99) with size range of 0.2–4.0 cm. The locations of the adenomas were 13 (48.1%) pancolonic, 6 (22.0%) transverse colon, 2 (7.4%) right colon, 2 (7.4%) left colon, and 4 (14.8%) site not specified at the first colonoscopy. One patient had 2 hyperplastic polyps with multiple adenomas; none had sessile serrated adenomas and one had colorectal cancer. Cumulatively, at last colonoscopy the mean number of adenomas was 51.3 ± 32.2 (range 10–99). The adenoma size range was 0.1–10cm at the last colonoscopy. The patient with the 10 cm polyp had colectomy for polyp removal. The locations of the adenomas were 10 (37.0%) pancolonic, 7 (25.9%) transverse colon, 3 (11.1%) right colon, 1 (3.70%) left colon, and 6 (22.2%) site not specified at the last colonoscopy.

Because of the variable time of follow-up between colonoscopies, the cumulative polyp number was calculated in 18 of 27 patients who had surveillance colonoscopies at 1 and 2 years from the first colonoscopy. In these patients, polyp number increased a mean of 2.8 ± 1.7 fold at 1 year and 4.2 ± 2.8 fold at 2 years from the first colonoscopy.

In 20 of the 27 patients (74%) the diagnosis of MCRA was made at the first colonoscopy. The other patients were diagnosed with MCRA in a subsequent surveillance colonoscopy.

Two of 27 patients (7.4%) had colorectal cancer diagnosed at colonoscopy. This included one patient diagnosed at first colonoscopy and one patient diagnosed on surveillance colonoscopy. Both patients had a first degree family history of CRC and MCRA. The first patient was a 34 year old woman who underwent first colonoscopy due to rectal bleeding. At that examination, the patient had multiple adenomas throughout the colon. Biopsy revealed tubulovillous adenomas and rectal adenocarcinoma. The patient underwent proctocolectomy with the resection specimen revealing stage 3 rectal adenocarcinoma. On EGD surveillance, she had fundic gland polyps and no polyps in the duodenum. Biopsy was taken at the papilla which revealed normal histological tissue. The second patient was a 70 year old man undergoing colonoscopy due to family history of CRC and change of bowel habit. On examination, there were multiple adenomas (up to 90) and a mass in the ascending colon. Biopsy of the mass revealed tubulovillous adenoma with low-grade dysplasia and colectomy with the surgical specimen revealed adenocarcinoma (T1, N0, M0).

Nineteen of 27 patients (70%) underwent EGD at an average age of 48.6 ± 12.6 (range 26 – 74) years (Table 3). The indications for EGD were screening for upper tract polyps in fifteen (73.6%), unabating symptoms of gastroesophageal reflux in two (10%), gastrointestinal bleeding in one (5%), and abdominal pain in one (5%). Of these, 9 patients (47%) had upper tract findings including 4 (21%) with duodenal adenoma, 3 (10%) with fundic gland polyps (all of which were on proton-pump inhibitors), and 2 (10%) with both duodenal adenoma and fundic gland polyps. Fundic gland polyps were located in the gastric body and fundus with the number ranging between 1–6. MCRA patients with negative EGD findings had EGD at a mean age of 52.0 ± 14.0 years in comparison to MCRA patients with abnormal EGD findings with mean age of 45.1 ± 10.5 years (p value = 0.25). The mean number of colorectal polyps of MCRA patients with negative upper GI findings and those with upper GI findings were 36.3 and 54.9, respectively (p value = 0.3). Patients with upper GI tract

findings were diagnosed with MCRA at significantly younger age compared to those without findings (40.3 vs 50.6 years; $p<0.05$).

Eighteen of 27 patients (67%) underwent surgery at mean age 51.4 ± 15.9 years with mean time from diagnosis of MCRA of 3.1 ± 1.3 years (Table 4). The indications for surgery were: polyps too numerous to remove endoscopically in 16 patients, adenoma with high-grade dysplasia in 1 patient, and right colon mass in 1 patient. After surgery, sixteen patients (88%) had endoscopic surveillance of the retained colorectum. Two surveyed patients developed recurrent adenomas in the retained colorectum with a mean follow up time of 11.5 years. None developed serrated polyps in the retained colorectum.

Nine patients of 27 (33%) had extracolonic cancers including nonmelanoma skin cancer (4), melanoma (3), and leukemia, breast, bladder and prostate cancer in one each. One patient had both nonmelanoma skin cancer and bladder cancer. Table 5 shows extracolonic manifestations/cancers per three subgroups of cumulative number (range) of adenomas. No distinct associations could be made. Malignant skin cancers manifested in all subgroups.

DISCUSSION

Few data exist on clinical features of MCRA patients not diagnosed with AFAP or MAP. The present study evaluated the colorectal phenotype and clinical characteristics of MCRA patients. These individuals were monitored, but not as part of a protocol, by serial colonoscopy with an average follow up of 4.91 years (range 0–27). Although not part of a formal protocol, endoscopists removed all polyps during each colonoscopy except when there were too many to be removed and patients were immediately sent for colectomy.

The mean age at diagnosis of MCRA in our study was 50.4 years with one case diagnosed at 21 years old. This finding is similar to two other reports of MCRA (7, 8) with patients diagnosed at ages 50 and 60 years old. In our cohort, colorectal cancer screening guidelines appeared to influence the age of diagnosis since the majority of patients were diagnosed at screening colonoscopy. The mean number of adenomas at MCRA diagnosis in our cohort was 40.1. The diagnosis of MCRA was reported at later age by Thirlwell et al. (60 years old) and a mean number of adenomas at diagnosis of 24 (7). In the current study, 6 of 27 patients (22%) had a first-degree relative with MCRA and 13 of 27 patients (48%) had a first degree relative with CRC. This is similar to several other investigations (7–9).

MCRA patients had upper gastrointestinal tract findings which can also be found in attenuated FAP and MAP patients (6, 10–12). In the current study, 19 patients underwent EGD at a mean age of 48.6 years. Nine patients had gastric fundic gland polyps, duodenal adenomas or both. However, Thirlwell et al. reported no upper gastrointestinal findings and absence of extracolonic tumors in this study (7). In addition, we noted extracolonic malignancies of the skin, breast and bladder in MCRA patients that have also been noted in MAP patients (11). We did not note any brain or thyroid malignancies that are typically associated with FAP.

The findings in this retrospective investigation are limited by several considerations. A small number of patients were evaluated in this study. Although complete information was

obtained and verified on all participants, the accuracy of the data depended on the medical record. In our investigation, the patients came to a specialized center for management, and, consequently, the element of referral bias cannot be discounted.

Recently, mutations in DNA polymerase ε (POLE) and δ (POLD1), which function as proofreading repair during DNA replication, have been identified in families with multiple colorectal adenomas and CRC (13). Although POLE and POLD1 may play a role in MCRA, it is unlikely to be a common cause. In a series of polyposis patients evaluated, only one out of 191 polyposis patients had a POLE mutation (13). Additionally, in literature reports, pedigrees with POLE mutation demonstrated an autosomal dominant transmission pattern, which was not seen in our families. Consequently, POLE mutation is unlikely to be the cause of MCRA in most of the patients. The patients were not evaluated for the promoter and splice site regions; thus, there is a possibility that *APC* promoter 1B mutations could be found in mutation-negative FAP patients. In regards to other etiologic possibilities of MCRA patients without germline mutations, cryptic and other APC and MYH gene mutations are one possibility, as well as other yet unidentified polyposis genes.

In summary, MCRA patients have a clinicopathological phenotype similar to the known syndromes of attenuated adenomatous polyposis presenting with polyps at middle age, continuous development of adenomas, lack of serrated polyp histology, presence of upper GI polyps in many patients, family history of the disorder in some patients, and the need for colectomy in the majority. Thus, the management of these patients and families should parallel the treatment of those with AFAP and MAP. This includes routine surveillance of the upper tract, consideration for colectomy when colonoscopic treatment is ineffective, and surveillance of retained colorectum after surgery. Lastly, with the rapid pace of scientific discovery, these patients should be advised to return intermittently for follow-up to reconsider if additional genetic testing is available, and if management recommendations have changed.

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Abbreviations

MCRA	multiple colorectal adenomas
SD	Standard Deviation
MAP	*MUTYH*-associated polyposis
FAP	familial adenomatous polyposis

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics 2010. CA Cancer J Clin. 2010; 60(5):277–300. [PubMed: 20610543]
2. American Society of Clinical O. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. 2003; 21(12):2397–2406. [PubMed: 12692171]
3. Lipton L, Tomlinson I. The genetics of FAP and FAP-like syndromes. Fam Cancer. 2006; 5(3):221–226. [PubMed: 16998667]
4. Leppert M, Dobbs M, Scambler P, et al. The gene for familial polyposis coli maps to the long arm of chromosome 5. Science. 1987; 238(4832):1411–1413. [PubMed: 3479843]
5. Lagarde A, Rouleau E, Ferrari A, et al. Germline APC mutation spectrum derived from 863 genomic variations identified through a 15-year medical genetics service to French patients with FAP. J Med Genet. 2010; 47(10):721–722. [PubMed: 20685668]
6. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. Nat Genet. 2002; 30(2):227–232. [PubMed: 11818965]
7. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA. 2012; 308(5):485–492. [PubMed: 22851115]
8. Thirlwell C, Howarth KM, Segditsas S, et al. Investigation of pathogenic mechanisms in multiple colorectal adenoma patients without germline APC or MYH/MUTYH mutations. Br J Cancer. 2007; 96(11):1729–1734. [PubMed: 17505512]
9. Filipe B, Baltazar C, Albuquerque C, et al. APC or MUTYH mutations account for the majority of clinically well-characterized families with FAP and AFAP phenotype and patients with more than 30 adenomas. Clin Genet. 2009; 76(3):242–255. [PubMed: 19793053]
10. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol. 2006; 101(2): 385–398. [PubMed: 16454848]
11. Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology. 2009; 137(6):1976–1985. e1–e10. [PubMed: 19732775]
12. Jasperson KW, Tuohy TM, Neklason DW, et al. Hereditary and familial colon cancer. Gastroenterology. 2010; 138(6):2044–2058. [PubMed: 20420945]
13. Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013; 45(2): 136–144. [PubMed: 23263490]

Table 1

Characteristics of Colonoscopy Evaluations

Characteristics	
Total number of colonoscopies	93
Median (range) number of colonoscopies per patient	3 (1–9)
Mean ±SD (range) age at first colonoscopy (years)	47.7 ± 13.1 (21–72)
Mean ±SD (range) age at last colonoscopy (years)	52.6 ± 12.2 (21–74)
Mean (range) follow-up (years)	4.90 (0–27)
Mean (range) colonoscopy surveillance interval (years)	1.06 (0–8)

EGD, esophagogastroduodenoscopy

Table 2

Mean Cumulative Number (range) of Polyps Found on Colonoscopy

	Hyperplastic	SSA/P	Tubular Adenoma	Tubulovillous Adenoma	CRC	Total Adenomas
First Colonoscopy *	0.15 (0–2)	0	33.6 (0–99)	1.33 (0–20)	0.04 (0–1)	35.0 (0–99)
Diagnostic Colonoscopy ¥	0.37 (0–3)	0.04 (0–1)	38.1 (0–99)	1.52 (0–20)	0.04 (0–1)	40.1 (10–99)
Last Colonoscopy	0.44 (0–3)	0.04 (0–1)	49.0 (0–99)	1.70 (0–20)	0.04 (0–1)	51.3 (0–99)

* First colonoscopy that patient ever had.

¥ Colonoscopy at which the diagnosis of multiple colorectal adenomas (MCRA) was made. SSA/P = sessile serrated adenoma/polyp. CRC = colorectal cancer

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Table 3

Characteristics of Patients Undergoing Esophagogastroduodenoscopy (EGD)

	Normal EGD	Abnormal EGD	P value
Number of Patients (n)	10	9	
EGD Results:			
Duodenal adenomas	NA	4	
Fundic gland polyps	NA	3	
Duodenal adenomas and fundic gland polyps	NA	2	
Mean Age ± SD (range) at EGD finding (years)	52.0 ± 14.0 (26–74)	45.1 ± 10.5 (30–61)	0.25
Mean Age ± SD (range) of MCRA diagnosis (years)	50.6 ± 14.5 (21–73)	40.3 ± 11.9 (25–58)	0.02
Mean Number of Polyps ± SD (range) at MCRA diagnosis	36.3 ± 31.9 (12–99)	54.9 ± 43.4 (10–99)	0.3

EGD, esophagogastroduodenoscopy; NA, non-applicable
MCRA, multiple colorectal adenomas

Table 4

Characteristics of Patients Undergoing Surgery for MCRA

Characteristic	
No (%) of patients undergoing surgery	18 (67)
Mean ± SD age at diagnosis of MCRA (years)	48.3 ± 14.6 (21–72)
Mean ± SD age at surgery (years)	51.4 ± 15.9 (21–72)
Type of surgery, n (%)	
Colectomy with ileorectal anastomosis	12 (66)
Right hemicolectomy	2 (11)
Laparoscopic proctocolectomy with ileoanal pouch and diverting ileostomy	1 (5.5)
Total protocolectomy with ileostomy	3 (16)
Patients with endoscopic surveillance after surgery, n (%)	16 (88)
Patients with recurrent adenomas, n (%)	2 (12.5)

SD, standard deviation
MCRA, multiple colorectal adenomas

Table 5

Extracolonic Manifestation/Cancer in Association to Subgroups of Cumulative Number of Adenomas

	Cumulative Number (range) of Adenomas		
	10--30	**31--60**	**61--99**
Number of Patients (n)	16	5	6
Extracolonic Manifestation/Cancer	Melanoma; basal cell cancer; lipoma; breast cancer; bladder cancer; multiple sebaceous cysts	Melanoma; supernumerary teeth; lipoma; prostate cancer	Melanoma; hairy cell leukemia and basal cell carcinoma; osteoma
Patients Treated with Surgery	8	4	6