Published in final edited form as:
Dis Colon Rectum. 2013 November ; 56(11): . doi:10.1097/DCR.0b013e3182a11cca.

Serrated polyposis: Colonic phenotype, extra-colonic features and familial risk in a large cohort

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Abstract

BACKGROUND—Serrated polyposis is a poorly understood and likely under-diagnosed condition. Little is known regarding the colorectal cancer risk, extra-colonic phenotype, and etiology of serrated polyposis.

OBJECTIVE—The aim of this study is to describe the clinical and family history features of a large cohort of individuals with serrated polyposis.

DESIGN—This is a retrospective cohort study from two prospectively collected registries.

PATIENTS—Patients meeting the updated 2010 World Health Organization criteria for serrated polyposis.

MAIN OUTCOME MEASURES—We report descriptive statistics for clinical and family history factors.

RESULTS—A total of 52 individuals met criteria for serrated polyposis. Of these, one had Lynch syndrome and was not included in the statistical analyses. Median age at serrated polyposis diagnosis was 51 years (range 18–77). Twenty four (47%) were male and 25 (49%) had a history of smoking. Two-hundred sixty-eight lower endoscopic procedures were performed; 42 (82%) had colorectal adenomas, 8 (16%) had a personal history of colorectal cancer (only one was diagnosed during follow-up), 12 (24%) had extra-colonic tumors (4 had more than one primary tumor), and 19 (37%) reported a family history of colorectal cancer. Esophagogastroduodenoscopy in 30 individuals revealed only one (3%) with unexplained gastroduodenal polyps. No association was found between colorectal cancer diagnosis and sex, age at serrated polyposis diagnosis, extra-colonic tumor, history of adenoma, or smoking status.

LIMITATIONS—This was a retrospective study with no comparison groups.

CONCLUSIONS—Gastroduodenal polyps are uncommon and likely not associated with serrated polyposis. Although extra-colonic tumors were common in our cohort, it is still unclear whether these are associated with serrated polyposis. Our data, along with previous studies, support an association between serrated polyposis and smoking. Further work is still needed to clarify the effect of smoking on polyp development/progression in serrated polyposis.

Keywords

Serrated polyposis; hyperplastic polyposis; sessile serrated adenoma; colon polyps; colorectal cancer

INTRODUCTION

Growing evidence supports that 15–20% of colorectal cancers (CRCs) arise through the serrated pathway, which is characterized by widespread gene inactivation via hypermethylation of promoter regions (the CpG island methylator phenotype), *BRAF* mutations, and frequent microsatellite instability.[1] The precursor lesion in this pathway is a type of serrated polyp.[1] At least three distinct serrated polyps have been described, including hyperplastic polyps, sessile serrated polyps (also referred to as sessile serrated adenomas), and traditional serrated adenomas, all of which share a saw-toothed or serrated histologic appearance.[2] Serrated polyposis (SP), previously known as hyperplastic polyposis, is a relatively rare CRC predisposition. As the name implies, SP is characterized by multiple serrated polyps. The genetic basis remains unknown; therefore, the World Health Organization (WHO) developed consensus criteria for a clinical diagnosis of SP and updated it in 2010 (Table 1).[2]

Studies reporting on the prevalence of CRC in patients with SP range from no cases of CRC to as many as 77%.[3] Similarly, a family history of CRC is reported in zero to 59% of SP cases.[3] Moreover, it is not clear why the personal and family history of CRC is so divergent among studies. Also, very little is known regarding the extra-colonic phenotype associated with SP.

In this study we describe the clinical characteristics and family history of a large cohort of patients meeting the most recent (2010) WHO criteria for a diagnosis of SP during multiple years of endoscopic surveillance. We first report on the clinical characteristics, including the proportion of SP patients with a CRC diagnosis, with a family history of CRC, or a diagnosis of an extra-colonic tumor. We then present the associations of clinical characteristics for SP cases with and without a diagnosis of CRC.

METHODS

Patients

Patients meeting criteria for SP were ascertained by searching two cancer genetic registries through Huntsman Cancer Institute (HCI) at the University of Utah. These registries include practically all patients evaluated in a cancer genetics clinic at HCI due to their personal history of colon polyps/cancer and then enrolled into a registry with a cancer genetics focus. Patients may also have been self-referred or referred by an internal HCI or external healthcare provider to one of the registries due to their personal/family history of cancer/polyps. Patients were enrolled in one of the registries from February 2000 to April 2012.

Patients were eligible for this study if they met WHO criteria I and/or III for SP, as outlined in Table 1. None of the patients were included on the basis of meeting WHO criterion II only, as this criterion mainly pertains to family history and has not been included in other large studies of SP. This study was approved by the University of Utah Institutional Review Board.

Data collection and analysis

Demographic information, endoscopy procedures (colonoscopy, sigmoidoscopy and esophogastroduodenoscopy (EGD)), surgery reports, clinic notes, histopathology reports and family history were abstracted from the medical record and/or registry databases/charts. Abstracted information included: sex, age at SP diagnosis, dates of endoscopies and colorectal surgeries, number/type/location of colorectal polyps, presence of CRC, age at CRC diagnosis and location, family history of CRC in 1st and/or 2nd degree relatives and personal history of extra-colonic tumors/cancers. Smoking status was recorded as current (at time of SP diagnosis), never (never smoked or smoked less than 100 cumulative cigarettes), or ever (smoked at least 100 cumulative cigarettes but not at the time of SP diagnosis).

Polyp type and number were abstracted from the pathology, endoscopy, and/or surgery reports. Serrated polyps were counted as such only when confirmed by histopathology. Total serrated polyp count was determined by adding the specific number and types reported in reports. Non-specific polyp counts listed in the medical record, such as “multiple”, “few”, “numerous”, or “many” were handled conservatively. For example, if multiple polyps were reported in the endoscopy report and only two biopsies of polyps were taken and confirmed to be hyperplastic polyps, only two total serrated polyps would be counted. If “many polyps” were described with 10 biopsies and a mixture of hyperplastic and adenomatous polyps were found, we could not determine how many polyps were hyperplastic and how many were adenomatous; therefore, only one serrated polyp could be confirmed and counted towards the total number of serrated polyps. Given this method, the total serrated polyp count is likely an underestimate of the total number of serrated polyps for each individual. However, the total number of all polyps seen in each individual accounts for the confirmed serrated polyps plus the remaining polyps described in the endoscopy report (whether or not they were confirmed by histopathology). For example, if 10 polyps were documented in the endoscopy report and there is one biopsy proven hyperplastic polyp and one adenoma confirmed, 10 polyps were still counted toward the “total polyp” count, but only one polyp would be counted toward the “total serrated polyp” count.

We also determined how many individuals had serrated polyps greater than or equal to 10 mm in size, as this was a commonly used size designation in endoscopy reports obtained in our study. However, in order for patients to meet SP criterion I, we used the strict WHO criteria which required at least five serrated polyps proximal to the sigmoid colon with at least two greater than 10 mm. Serrated polyps were grouped together and not listed out separately, as the distinction among hyperplastic polyps, sessile serrated polyps and traditional serrated adenomas has only recently been recognized and endoscopy reports in this study go back to as early as 1990. Analysis represents data up to April 2012.

We calculated descriptive statistics for the clinical and demographic variables of interest. We report mean (standard deviation), median (range) and the proportion reporting each variable of interest as relevant. P-values were calculated using t-test and chi-square statistics. Statistical analyses were performed in Stata 12.

RESULTS

In total, 52 individuals met SP criteria. One of these individuals also had a deleterious mutation in *MLH1* (Q490X), confirming a molecular diagnosis of Lynch syndrome. This individual was initially diagnosed with cancer of the cecum at 32 followed by a right hemicolectomy. Over the next 12 years he underwent at least 15 colonoscopies and was found to have approximately 55 serrated polyps in the rectum to descending colon (majority of polyps were located in the rectum and confirmed to be hyperplastic polyps), 3 adenomatous polyps, a 15 mm adenomatous polyp with high grade dysplasia, and a poorly

differentiated mucinous adenocarcinoma of the splenic flexure at age 44. Although colectomy was advised before the diagnosis of colon cancer at age 44, he chose to continue with surveillance until his second colon cancer occurred. He then underwent completion colectomy with ileorectal anastomosis. Since that time he has undergone 8 sigmoidoscopies and multiple rectal hyperplastic polyps have been confirmed. In addition, a sigmoidoscopy at age 46 revealed a stage I small bowel adenocarcinoma 70 cm proximal from the anus. Due to his history of known Lynch syndrome, this individual was not included in the statistical analyses reported in this study and is only described in the text. Therefore, 51 patients were included in the statistical analyses.

Demographic and clinical characteristics of the 51 patients are shown in Table 2. The median age at diagnosis of SP was 51 years (range 18–77) while the mean was 49 years. The median follow-up time from first to last known sigmoidoscopy/colonoscopy was 61 months (~5 years) with a range of zero to 217 months (18 years 1 month). There were 24 (47%) males and 27 (53%) females. The vast majority of patients were white (96%). A total of 25 (49%) were current or former cigarette smokers. Patients underwent their first colonoscopy for a variety of reasons including; routine screening (22%), hematochezia (34%), family history of CRC (14%), or abdominal pain/diarrhea (30%). Patients underwent a total of 268 colonoscopy/sigmoidoscopy procedures, with a median of 5 (range 1–11) procedures.

The colonic phenotype of the 51 SP patients is outlined in Table 3. Concomitant adenomas were common (82%) and the vast majority (71%) had at least one serrated polyp greater than or equal to 10 mm in size. The median number of serrated polyps was 35 (range 8–180) and the median number of total polyps was 53 (range 9–277). Eight patients (16%) had a personal history of CRC. Of these, six were located proximal to the sigmoid colon, one in the distal colon, and one was unknown. The youngest age of CRC diagnosis was 22 years. CRC was diagnosed before (range 1 to 34 years prior) or at the same time as the diagnosis of SP in 7 of the 8 (88%) individuals. The remaining individual was diagnosed with CRC during surveillance approximately two years after the diagnosis of SP. Nineteen (37%) individuals reported a family history of CRC in first and/or second-degree relatives, with 12 (24%) having at least one first degree relative with CRC and 10 (20%) having at least one second degree relative affected. Four (8%) had a first- and/or second-degree relative diagnosed with CRC at age less than 50.

Five (10%) individuals reported a family history of a relative having greater than or equal to 5 colorectal polyps. One individual had a sibling with CRC at age 36 in addition to approximately 50 adenomatous polyps confirmed by medical records. To our knowledge, genetic testing for an adenomatous polyposis condition has not been performed in this family. Another individual had a sibling with 8 hyperplastic polyps (did not meet SP criteria I or III) that were confirmed with medical records, another individual had a sibling with greater than 10 hyperplastic polyps (did not meet SP criteria I or III) confirmed by medical records, and another individual had a mother and maternal grandmother with 10–30 polyps however, medical records confirming the specific polyp type, number, size, and location were not available.

Twelve (24%) patients had a personal history of extra-colonic tumor/s. The age at last known contact with the patient, the tumor types, and ages of onset for each patient are listed in Table 4. Five individuals had more than one primary tumor; one of these individuals had four separate primaries and another had five primaries. The patient with five separate primaries was thought to have a treatment induced meningioma as she had radiation therapy as a child for her ependymoma. Skin cancer occurred in six patients, while breast cancer occurred in three patients, both of which are common in the general population. Rare tumors were also seen, such as a paraganglioma and an ependymoma.

In total, 30 individuals underwent EGD and none were found to have duodenal polyps or gastric adenomas. Three (10%) were found to have gastric fundic gland polyposis, however two of these individuals had a history of proton pump inhibitor use. One individual with fundic gland polyposis (at least 30 polyps were documented) did not report a history of proton pump inhibitor use.

In total, 49% of the patients were current or former smokers. No association was found between personal history of CRC and age at SP diagnosis, gender, smoking status, history of adenoma, family history of CRC, or personal history of extra-colonic tumor (Table 5).

DISCUSSION

SP is an under recognized entity in gastroenterology practices[4] and its natural history and phenotype have not been well characterized. Our study evaluated the phenotypic characteristics of a large cohort of patients meeting recently updated WHO criteria for a diagnosis of SP. The mean age at diagnosis of SP was 49 years, which is similar to prior studies reporting between 49 and 56 years.[5,6] The youngest patient diagnosed with SP in our study was 18 years. Others have reported young age of onset in a minority of patients with 10 years being the youngest.[7]

CRC development in SP is likely influenced by many different factors, most of which are currently not known or well understood. Our sample had a 16% prevalence of CRC. Other studies have reported that between zero to 77% of SP patients had CRC.[3,8] Only one (2%) patient in our study was diagnosed with CRC after the diagnosis of SP. Boparai et al (2010) found a higher prevalence of CRC (5 of 77 (6.5%)) after the diagnosis the diagnosis of SP.[9] This study also revealed that the number of serrated polyps is positively correlated with CRC.[9] Specifically, the risk of CRC increased by 5% and 9% with each additional hyperplastic polyp and serrated adenoma, respectively.[9] Of the 77 patients with SP in their study, 1,984 polyps were identified and 27 (35%) had CRC. In our cohort, we found more polyps (2,379 serrated polyps and 3,574 total polyps) but fewer CRCs than Boparai et al. (2010). The low prevalence of CRC may in part be due to the short interval of colonoscopies performed in our study, as we recommend patients meeting SP criteria undergo colonoscopies every 1–2 years.

In our cohort, 49% of SP patients were current or former smokers, which is higher than the overall prevalence rate of 27.8% of ever smokers in Utah.[10] It is likely that cigarette smoking has an effect on polyp development in patients with SP. Smoking has been linked to SP in other studies, although it is still not clear the exact effect smoking has on colon polyp and cancer development.[11] CRC development in SP is complex and differences in patient populations, study methods, and other confounding factors may influence the wide range of CRC rates reported in the literature. Further work is needed in this area to better understand how these different factors may influence CRC risk in SP.

Extra-colonic tumors/cancers are a feature of most hereditary CRC syndromes. Currently the data supporting an association between SP and extra-colonic tumor risk is lacking. In our cohort, only 1 of 30 (3.3%) patients who underwent EGD was found to have unexplained gastric fundic gland polyposis and none had duodenal polyps or gastric adenomas. This supports prior studies that individuals with SP are not at increased risk for gastroduodenal polyps.[6] In our cohort, 24% had a history of an extra-colonic cancer/tumor, however a number of these tumors are common in the general population (breast cancer and skin cancer). We report on the first ever known case of paraganglioma diagnosed in an individual meeting criteria for SP. A prior cohort study from Cleveland Clinic also found 28% of their patients had a history of extra-colonic cancer with prostate being the most common.[12]

Currently, the extra-colonic tumors reported in patients with SP in various studies are not consistent. This makes it difficult to determine if individuals with SP are at increased risk for extra-colonic tumors or whether these tumors occurred by chance or were referred due to their tumor history. Even though our patients were routinely enrolled in a registry due to their personal history of colon polyps, as with other studies, we cannot exclude the possibility of referral bias.

Thirty seven percent of patients in our study reported a family history (first and/or second-degree) of CRC. Other studies have found a family history of CRC reported in zero to 59% of SP cases.[3] The reasons for the high variability in reported family history of CRC is largely unknown. Selection bias may be a playing a role in some of these studies. A greater than fivefold increased risk of CRC has also been noted in first-degree relatives of patients with SP.[5,13] Prior studies have also demonstrated 5% of reported families had at least one first-degree family member with a diagnosis of SP in addition to the index patient.[5,7] Pedigree aggregation with possible dominant inheritance is also reported in five other cases.[14–16] Despite the lack of an identified genetic cause as of yet, these data support the theory that inheritance may play a role in some cases of SP. These data should still be interpreted with caution as they are also susceptible to biases.

In a small cohort of 17 patients with MUTYH-associated polyposis (MAP), three (18%) met criteria for SP.[17] Other case reports of MAP and SP have been documented, but are uncommon.[7,18] Although we did not have any known MAP cases in our cohort, this was not systematically studied and most patients did not meet clinical criteria for *MUTYH* genetic testing. We did identify one patient with Lynch syndrome and SP. To the authors' knowledge, this is the first ever reported case of Lynch syndrome meeting WHO criteria for SP. Jarrar et al. (2009) identified 12 patients from 7 families meeting clinical criteria for SP and familial CRC/Amsterdam criteria (clinical criteria used to evaluate for Lynch syndrome).[19] However, none of these individuals or families was confirmed to have a germline mutation and therefore Lynch syndrome could not be proven in this study. It is still unclear whether there is an association between Lynch syndrome and SP, however, with this being the first reported case in the literature, it is unlikely that there is a strong association between the two.

One potential bias in our study is that patients were obtained through a cancer genetic registry. Therefore, higher risk patients may be included in our study compared to individuals identified through a gastroenterology screening practice. Even though a small number of patients were evaluated, this is still one of the largest studies of SP to date in the world.

Our study adds to the literature regarding the natural history of SP. Healthcare providers need to be aware of this condition and recognize the association with CRC so that appropriate surveillance strategies can be offered to patients and CRC can be prevented. Our results along with other studies to date on SP support the use of colonoscopy surveillance every 1–2 years in patients with intact colons with removal of polyps at time of procedure, similar to guidelines used in the adenomatous polyposis syndromes. Surgical management must be considered when polyps cannot be controlled endoscopically and the decision for colectomy should be individualized for each patient based on the results of their surveillance colonoscopies. Our data and others do not support surveillance EGDs in SP. Unlike other studies, extra-colonic cancers were more common than CRCs in our cohort. Further work is needed before any conclusions can be drawn regarding extra-colonic tumor risk in SP. Lastly, Lynch syndrome and SP are not mutually exclusive, though it is still not clear whether germline mismatch repair mutations predispose to SP.

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Table 1

WHO clinical diagnostic criteria for serrated polyposis

Individuals meeting any of the following criteria	
I.	>≥ five serrated polyps proximal to the sigmoid colon with at least two greater than 10 mm
II.	at least one serrated polyp proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
III.	> 20 serrated polyps of any size, but distributed throughout the colon

Table 2

Demographic and clinical characteristics of patients with SP (n=51)

Age at SP diagnosis, median (range)	51 (18–77)
Sex, n (%)	
Female	27 (53)
Male	24 (47)
Race/Ethnicity, n (%)	
White	49 (96)
Hispanic	1 (2)
Ashkenazi Jewish	1 (2)
Smoking status, n (%)	
Never	26 (51)
Current	15 (29)
Ever	10 (20)
Indications for surveillance colonoscopy, n (%)*	
Screening	11 (22)
Hematochezia	17 (34)
Family history of CRC	7 (14)
Other (diarrhea, abdominal pain)	15 (30)
Median follow-up time in months (range)	61 (0–217)
Number of colonoscopies/sigmoidoscopies, median (range)	5 (1–11)

*Colonoscopy indication missing for 1 participant

Table 3

Colonic phenotype of study patients with SP (n=51)

Patients with adenomas, n (%)	42 (82)
Patients with a serrated polyp ≥ 10 mm, n (%)	36 (71)
Number of serrated polyps, median (range)	35 (8–180)
Number of total polyps, median (range)	53 (9–277)
Patients with colorectal cancer (CRC), n (%)	8 (16)
Location of CRC	
Proximal CRC, n (%*)	6 (86)
Distal CRC, n (%*)	1 (14)
Age in years at CRC diagnosis, median (range)	48 (22–72)
Family history of CRC	
Any, n (%)	19 (37)
First-degree relative, n (%)	12 (24)
Second-degree relative, n (%)	10 (20)
First- or second-degree relative < 50 years old, n (%)	4 (8)
Family history of ≥ 5 polyps either first or second-degree relative, n (%)	5 (10)

*Location of one CRC missing, n = 7 used for location percentages

Table 4

Extra-colonic tumors/cancers

Study ID #	Age at last contact	Sex	CRC diagnosis	Total # extra-colonoic tumors	Extra-colonic tumor/cancer history (age of diagnosis)
84735	59	F	N	2	Breast cancer (51); melanoma (56)
49309	50	F	N	1	Non-melanoma skin cancer (48)
31124	36	F	N	5	Ependymoma (4); meningioma (22); non-melanoma skin cancer (29, 35, and 35 all separate primaries)
72194	32	F	N	1	Non-melanoma skin cancer (30)
18004	32	F	N	1	Hodgkin lymphoma (13)
41057	67	F	N	2	Breast cancer (53); squamous cell carcinoma of the skin (66)
41053	68	M	N	1	Non-melanoma skin cancer (50)
51667	48	F	N	4	Hodgkin lymphoma (19), hurthle cell thyroid cancer (42), breast cancer (45), non-melanoma skin cancer (?)
63833	75	M	N	2	Melanoma (58); prostate cancer (71)
10002002	75	F	N	2	Carotid body paraganglioma (73)
41060	54	F	N	1	Cervical cancer (37)
41171	74	F	Y	1	Papillary thyroid cancer (63)

F=female; M=male; CRC=colorectal cancer

Dis Colon Rectum. Author manuscript; available in PMC 2014 November 01.

Table 5

CRC in SP compared with patient and family characteristics

	CRC diagnosis	No CRC diagnosis	P-value*
Age at SP diagnosis, mean (SD)	55 (19)	47 (20)	0.31
Gender, n (%)			
Male	2 (25)	22 (51)	0.26
Female	6 (75)	21 (49)	
Smoking status, n (%)			
Current/Ever	2 (25)	23 (53)	0.25
Never	6 (75)	20 (47)	
Personal history adenoma, n (%)			
Yes	7 (87.5)	34 (79)	> 0.50
No	1 (12.5)	9 (21)	
Extra-colonic tumors, n (%)			
Yes	1 (13.5)	11 (26)	> 0.50
No	7 (87.5)	32 (74)	
Family history of CRC, n (%)			
Yes	2 (25)	17 (40)	> 0.50
No	6 (75)	26 (60)	

CRC=colorectal cancer; SP=serrated polyposis

*p-value for continuous variables calculated using Students' t-test statistics and for categorical variables using Fisher's exact test