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Serrated Polyposis: Colonic Phenotype, Extracolonic Features, and Familial Risk in a Large Cohort
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Abstract
BACKGROUND: Serrated polyposis is a poorly understood and likely underdiagnosed condition. Little is known regarding the colorectal cancer risk, extracolonic phenotype, and cause 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.

METHODS: This is a retrospective cohort study from 2 prospectively collected registries.

PATIENTS: Patients meeting the updated 2010 World Health Organization criteria for serrated polyposis were included.

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%) patients were male, and 25 (49%) had a history of smoking. Two hundred sixty-eight lower endoscopic procedures were performed; 42 (82%) patients had colorectal adenomas, 8 (16%) had a personal history of colorectal cancer (only 1 was diagnosed during follow-up), 12 (24%) had extracolonic tumors (4 had more than 1 primary tumor), and 19 (37%) reported a family history of colorectal cancer.

Esophagogastroduodenoscopy in 30 individuals revealed only 1 (3%) with unexplained gastroduodenal polyps. No association was found between colorectal cancer diagnosis and sex, age at serrated polyposis diagnosis, extracolonic 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 extracolonic tumors were common in our cohort, it is still unclear whether these were associated with serrated polyposis. Our data...
Growing evidence supports that 15% to 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), \textit{BRAF} mutations, and frequent microsatellite instability. The precursor lesion in this pathway is a type of serrated polyp. At least 3 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. Serrated polyposis (SP), previously known as hyperplastic polyposis, is a relatively rare CRC predisposition. At 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).

Studies reporting on the prevalence of CRC in patients with SP range from no cases of CRC to as many as 77%. Similarly, a family history of CRC is reported in 0% to 59% of SP cases. 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 extracolonic 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 extracolonic tumor. We then present the associations of clinical characteristics for SP cases with and without a diagnosis of CRC.

**METHODS**

**Patients**

Patients meeting the criteria for SP were ascertained by searching 2 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 owing 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 health care provider to one of the registries because of 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, because 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 esophagogastroduodenoscopy (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 first- and/or second-degree relatives, and personal history of extracolonic 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
histopathology. Total serrated polyp count was determined by adding the specific number and types reported in reports. Nonspecific 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 2 biopsies of polyps were taken and confirmed to be hyperplastic polyps, only 2 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 1 serrated polyp could be confirmed and counted toward 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 1 biopsy-proven hyperplastic polyp and 1 adenoma confirmed, 10 polyps were still counted toward the “total polyp” count, but only 1 polyp would be counted toward the “total serrated polyp” count.

We also determined how many individuals had serrated polyps larger than or equal to 10 mm in size, because this was a commonly used size designation in endoscopy reports obtained in our study. However, for patients to meet SP criterion 1, we used the strict WHO criteria that required at least 5 serrated polyps proximal to the sigmoid colon with at least 2 larger than 10 mm. Serrated polyps were grouped together and not listed out separately, because 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. The analysis represents data up to April 2012.

We calculated descriptive statistics for the clinical and demographic variables of interest. We report mean (SD), median (range), and the proportion reporting each variable of interest as relevant. t values were calculated by using t test and [chi]2 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 age 32 followed by a right hemicolecctiony. 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 (the 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. Because of 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), whereas the mean age at diagnosis was 49 years. The median follow-up time from first to last known sigmoidoscopy/colonoscopy was 61 months (±5 years) with a range of 0 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 1 serrated polyp. We also determined how many individuals had serrated polyps larger than or equal to 10 mm in size, because this was a commonly used size designation in endoscopy reports obtained in our study. However, for patients to meet SP criterion 1, we used the strict WHO criteria that required at least 5 serrated polyps proximal to the sigmoid colon with at least 2 larger than 10 mm. Serrated polyps were grouped together and not listed out separately, because 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. The analysis represents data up to April 2012.
adenomas were common (62%), and the vast majority (71%) had at least 1 serrated polyp larger 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, 6 carcinomas were located proximal to the sigmoid colon, 1 in the distal colon, and 1 was unknown. The youngest age of CRC diagnosis was 22 years. CRC was diagnosed before (range, 1-34 years previously) 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 2 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 1 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 to 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 extracolonic tumors. 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 1 primary tumor; 1 of these individuals had 4 separate primary tumors and another had 5 primary tumors. The patient with 5 separate primary tumors was thought to have a treatment-induced meningioma, because she had radiation therapy as a child for her ependymoma. Skin cancer occurred in 6 patients, and breast cancer occurred in 3 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, 2 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, sex, smoking status, history of adenoma, family history of CRC, or personal history of extracolonic tumor (Table 5).

DISCUSSION

Serrated polyposis is an underrecognized entity in gastroenterology practices, 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 previous studies reporting between 49 and 56 years. 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.

Colorectal cancer 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 0% and 77% of SP patients had CRC. Only 1 (2%) patient in our study was diagnosed with CRC after the diagnosis of SP. Boparai et al. found a higher prevalence of CRC (5 of 77 (6.5%)) after the diagnosis of SP. This study also revealed that the number of serrated polyps is positively correlated with CRC. Specifically, the risk of CRC increased by 5% and 9% with each additional hyperplastic polyp and serrated adenoma. Of the 77 patients with SP in their study, 1984 polyps were identified and 27 (35%) had CRC. In our cohort, we found more polyps (2379 serrated polyps and
Of 10,000 colonoscopies performed, 2794 patients (27.9%) had CRC. In our cohort, we found more polyps (2379 serrated polyps and 3574 total polyps) but fewer CRCs than Boparai et al.9 The low prevalence of CRC may in part be due to the short interval of colonoscopies performed in our study, because we recommend that patients meeting SP criteria undergo colonoscopies every 1 to 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.

Extracolonic tumors/cancers are a feature of most hereditary CRC syndromes. Currently, the data supporting an association between SP and extracolonic tumor risk are 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 previous studies that individuals with SP are not at increased risk for gastroduodenal polyps.6 In our cohort, 24% had a history of an extracolonic 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 previous cohort study from Cleveland Clinic also found 28% of their patients had a history of extracolonic cancer with prostate being the most common.12 Currently, the extracolonic tumors reported in patients with SP in various studies are not consistent. This makes it difficult to determine whether individuals with SP are at increased risk for extracolonic tumors or whether these tumors occurred by chance or were referred owing to patients' tumor history. Even though our patients were routinely enrolled in a registry owing 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 0% 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 5-fold increased risk of CRC has also been noted in first-degree relatives of patients with SP.5,13 Previous studies have also demonstrated that 5% of reported families had at least 1 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 5 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 because they are also susceptible to biases.

In a small cohort of 17 patients with MUTYH-associated polyposis (MAP), 3 (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 1 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 al19 identified 12 patients from 7 families meeting clinical criteria for SP and familial CRC/Amsterdam criteria (clinical criteria used to evaluate for Lynch syndrome). 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 2.

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 with 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. Health care 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 detected at an early stage.
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 to 2 years in patients with intact colons with removal of polyps at the 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, extracolonic cancers were more common than CRCs in our cohort. Further work is needed before any conclusions can be drawn regarding extracolonic tumor risk in SP. Last, Lynch syndrome and SP are not mutually exclusive, although it is still not clear whether germline mismatch repair mutations predispose to SP.

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Serrated polyposis; Hyperplastic polyposis; Sessile serrated adenoma; Colon polyps; Colorectal cancer

### Table 1

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