

Colonic manifestations of *PTEN* hamartoma tumor syndrome: Case series and systematic review

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Received: July 28, 2013 Revised: September 12, 2013

Accepted: September 29, 2013

Published online: February 21, 2014

Abstract

AIM: To investigate our clinical experience with the colonic manifestations of phosphatase and tensin homolog on chromosome ten (*PTEN*) hamartoma tumor syndrome (PHTS) and to perform a systematic literature review regarding the same.

METHODS: This study was approved by the appropriate institutional review board prior to initiation. A clinical genetics database was searched for patients with PHTS or a component syndrome that received gastrointestinal endoscopy or pathology interpretation at our center. These patient's records were retrospectively reviewed for clinical characteristics (including family history and genetic testing), endoscopy results and pathology findings. We also performed a systematic review of the literature for case series of PHTS or component

syndromes that reported gastrointestinal manifestations and investigations published after consensus diagnostic criteria were established in 1996. These results were compiled and reported.

RESULTS: Eight patients from our institution met initial inclusion criteria. Of these, 5 patients underwent 4.2 colonoscopies at mean age 45.8 ± 10.8 years. All were found to have colon polyps during their clinical course and polyp histology included adenoma, hyperplastic, ganglioneuroma and juvenile. No malignant lesions were identified. Two had multiple histologic types. One patient underwent colectomy due to innumerable polyps and concern for future malignant potential. Systematic literature review of PHTS patients undergoing endoscopy revealed 107 patients receiving colonoscopy at mean age 37.4 years. Colon polyps were noted in 92.5% and multiple colon polyp histologies were reported in 53.6%. Common polyp histologies included hyperplastic (43.6%), adenoma (40.4%), hamartoma (38.3%), ganglioneuroma (33%) and inflammatory (24.5%) polyps. Twelve (11.2%) patients had colorectal cancer at mean age 46.7 years (range 35-62). Clinical outcomes secondary to colon polyposis and malignancy were not commonly reported.

CONCLUSION: PHTS has a high prevalence of colon polyposis with multiple histologic types. It should be considered a mixed polyposis syndrome. Systematic review found an increased prevalence of colorectal cancer and we recommend initiating colonoscopy for colorectal cancer surveillance at age 35 years.

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Key words: Adenoma; Bannayan-Riley-Ruvalcaba syndrome; Colon polyps; Colorectal cancer; Cowden syndrome; Endoscopy; Ganglioneuroma; Hamartoma; Hyperplastic; Phosphatase and tensin homolog on chromosome ten

Core tip: Phosphatase and tensin homolog on chromosome ten (*PTEN*) hamartoma tumor syndrome has a high rate of colonic polyposis. In contrast with prior dogma, the majority of patients will have mixed polyp histologies including adenoma, hamartoma and hyperplastic. Thus, multiple polyp types should spur investigation for this syndrome with a thorough clinical exam and possibly genetic testing. There is likely an increased risk of colorectal cancer at a young age and surveillance colonoscopy is recommended. We recommend starting at age 35 years.

Stanich PP, Pilarski R, Rock J, Frankel WL, El-Dika S, Meyer MM. Colonic manifestations of the *PTEN* hamartoma tumor syndrome: Case series and systematic review. *World J Gastroenterol* 2014; 20(7): 1833-1838 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i7/1833.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i7.1833>

INTRODUCTION

The phosphatase and tensin homolog on chromosome ten (*PTEN*) gene acts as a tumor suppressor through regulation of cell growth^[1]. The *PTEN* hamartoma tumor syndrome (PHTS) incorporates several rare diseases that occur secondary to germline mutations within the *PTEN* gene. The component syndromes include Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS), which many now consider a single entity with age-related phenotypic presentations^[2-5]. Lhermitte-Duclos disease (also known as dysplastic gangliocytoma of the cerebellum) and autism spectrum disorders with macrocephaly are variably included^[6,7]. The defining characteristic of PHTS is the development of hamartomas in multiple organ systems and an increased risk of malignancy, including breast, thyroid, endometrial, kidney and possibly melanoma^[8].

Cowden syndrome is thought to be the most common of the component syndromes, with an estimated prevalence of 1 in 200000-250000^[9]. A landmark study by Nelen *et al*^[10] in 1996 both localized the causative gene and described the first iteration of the International Cowden Consortium (ICC) diagnostic criteria, which included hamartomatous intestinal polyps as a minor criterion. The diagnostic criteria has since been revised, but there have been only minor changes and gastrointestinal (GI) hamartomas are still considered a minor criterion^[11].

Although Cowden syndrome and BRRS were known to have intestinal polyps as a manifestation, they were long thought to not infer an increased risk of malignancy due to the presumed hamartomatous nature of the polyps^[12]. However, this was based on case series compiled prior to modern flexible endoscopy and routine polypectomy. Recent work has begun to change this perception, with a higher rate of intestinal polyposis and an increased risk of colorectal cancer reported^[13,14]. This has led to a

change in the clinical guidelines by the National Comprehensive Cancer Network and the recommendation of endoscopic colorectal cancer surveillance^[15]. Unfortunately, beyond the risk of colorectal cancer minimal data are available regarding the clinical outcomes resulting from the intestinal polyposis, although one case series suggests colectomy may be more common than expected^[16].

The aim of the current study was to investigate our institution's experience with the gastrointestinal manifestations of PHTS and perform a systematic review of the modern literature with a similar focus.

MATERIALS AND METHODS

Case series

The appropriate institutional review board approved this study. An existing clinical genetics database was searched for patients that had been diagnosed with PHTS or a component syndrome including Cowden syndrome, BRRS or Lhermitte-Duclos disease and had a medical record number established at our institution. Forty-three patients were identified and their charts were retrospectively reviewed. Patients were evaluated further if they underwent an endoscopic evaluation or had intestinal tissue pathologic interpretation at our institution. Records were initially accessed on November 2, 2012 and any data collected after that point was censored. Exclusion criteria included insufficient documentation to confirm the diagnosis of PHTS or component syndrome. Eight patients met study criteria and were further characterized. Demographic data, including age at the time of initial procedure, manifestations of PHTS or component syndrome, family history, genetic testing results, endoscopic reports, surgical reports and pathology reports were collected. Estimation of colon polyp number and location were obtained directly from reports. Left-sided polyp location was considered when polyps were limited to distal to the splenic flexure. Pancolonic polyp location included polyps from both proximal and distal to the splenic flexure. Age is reported as mean \pm SD (range) in the text and mean in tables, number of procedures is reported as mean (range) in text and mean in tables. Other data are presented as proportions.

Systematic review

A systematic review of the medical literature for relevant case series of PHTS or component syndromes and GI manifestations that were published after the ICC diagnostic criteria were established was also performed^[10]. Inclusion and exclusion criteria were developed a priori. Inclusion criteria included the presentation of 3 or more patients with PHTS or a component syndrome published in a peer-reviewed journal with detailed information available regarding the endoscopic and GI pathologic investigations performed. Exclusion criteria included publication prior to 1996 and the presentation of 2 or fewer patients to limit ascertainment and publication bias. The literature search was independently performed by two authors (Stan-

Table 1 Clinical characteristics of the *PTEN* hamartoma tumor syndrome cohort receiving colonoscopy

	<i>n</i> (%)
Patients with colonoscopy	5
Female sex	5 (100)
Phenotype	
Cowden syndrome	5 (100)
BRRS	0 (0)
<i>PTEN</i> mutation	4 (80)
Family history of PHTS	2 (40)
ICC diagnostic criteria ¹⁰	
Pathognomonic	
Acral keratoses	1 (20)
Papillomatous lesions	0 (0)
Trichilemmomas	0 (0)
Major criteria	
Breast cancer	4 (80)
Dysplastic gangliocytoma of the cerebellum	0 (0)
Endometrial cancer	0 (0)
Macrocephaly	4 (80)
Thyroid cancer	1 (20)
Minor criteria	
Benign thyroid lesions	4 (80)
Fibroma	0 (0)
Fibrocystic breast disease	2 (40)
Genitourinary tumors	1 (20)
Hamartomatous intestinal polyps	1 (20)
Lipoma	3 (60)
Mental retardation	0 (0)

BRRS: Bannayan-riley-ruvalcaba syndrome; ICC: International cowden consortium; PHTS: *PTEN* hamartoma tumor syndrome.

ich PP and Pilarski R). Medline (<http://www.ncbi.nlm.nih.gov/pubmed/>), Scopus and the Cochrane library were searched using the strategy of: (*PTEN* OR Cowden* OR Bannayan-Riley-Ruvalcaba syndrome) AND (gastrointestinal OR polyp) with a limit of publication in 1996 or later. The reference sections of identified manuscripts were also searched for relevant reports. This was initially performed on January 22, 2013 and publications after this were censored. Five manuscripts were identified that met criteria^[14,16-19]. Data abstraction from the selected manuscripts was independently performed by two authors (Stanich PP and Meyer MM). Age and number of procedures were reported as means only given limitations of source material. In the tables with data acquired from the systematic literature review, information that was unavailable was demarcated “not reported” and excluded from the reported proportions.

RESULTS

Case series

Eight patients from our institution met inclusion criteria for the study and all were women. Six patients (75%) were consistent with a Cowden syndrome phenotype and 2 patients (25%) had a BRRS phenotype. All 8 patients underwent *PTEN* mutation testing and 7 (87.5%) were found to have deleterious mutations (3 deleterious nonsense mutations, 2 deleterious missense mutations and 2 with deleterious splice-site mutations). The patient without a

detected mutation met ICC diagnostic criteria for Cowden syndrome with macrocephaly, breast cancer, thyroid cancer, fibrocystic breast disease and lipomas. Three patients were from a single family and the others were unrelated.

Five patients (4 with *PTEN* mutation) from this cohort underwent colonoscopy at our institution. All were female and unrelated, with 4 (80%) Caucasian and 1 (20%) African-American. Further details regarding their PHTS clinical manifestations are included in Table 1. They underwent a mean 4.2 (range 1-10) colonoscopies, with the age at first procedure 45.8 ± 10.8 (range 33.8-63.7). Indications for initial colonoscopy were GI bleeding in 3 and to follow or confirm outside findings in 2.

All patients were noted to have polyps during their clinical course. Four patients had polyps on initial colonoscopy and 1 patient did not develop polyps until the third procedure at age 49.5 years (12 years after first colonoscopy). Among the patients with colon polyps on initial exam, 3 patients were reported to have “multiple” polyps without a numerical estimate and 1 patient had a single polyp identified.

Polypectomy was performed in 4 patients (1 patient with multiple polyps had no specimens removed due to anticoagulation and was then lost to follow-up). Histology included tubular and tubulovillous adenomas, hyperplastic, ganglioneuroma and a juvenile polyp (the ganglioneuroma and juvenile polyp occurred in the same patient). No malignant lesions were identified. Further details are reported in Table 2. One patient received a colectomy due to innumerable ganglioneuromatous colon polyps (estimated to be 200 on gross pathology examination) and concern for future malignant potential by providers, 3 patients underwent polypectomies during serial colonoscopies with complete clearance of polyps from colon and 1 patient was lost to follow-up.

Systematic review

Colon findings from the systematic literature review are reported in Table 2. Colonoscopy was performed in 107 patients at mean age 37.4. Ninety-nine (92.5%) had polyps and 64% of patients were estimated to have 50 or more polyps when the number of polyps were reported. They were most often pancolonic (71.4%) when location was described. There was a wide array of histologies, with PHTS patients having hyperplastic (43.6%), adenoma (40.4%), hamartoma (38.3%), ganglioneuroma (33%) and inflammatory (24.5%) polyps commonly reported. Many patients had more than a single histology, with 31% having 2 types and 22.6% having 3 or more types. Colorectal cancer was found in 12 patients (11.2% of total cohort, 12.8% of patients with pathology reviewed) with mean age 46.7 (range 35-62) years. Findings were similar when limited to patients with confirmed *PTEN* mutations.

DISCUSSION

Intestinal hamartomatous polyposis has been described as a feature of Cowden syndrome, Bannayan-Riley-Ruvalca-

Table 2 Colon findings from the *PTEN* hamartoma tumor syndrome cohort and systematic review

Author	OSU cohort	Levi <i>et al.</i> ^[19]	Coriat <i>et al.</i> ^[18]	Stanich <i>et al.</i> ^[16]	Heald <i>et al.</i> ^[14]	Kim <i>et al.</i> ^[17]	Total, all patients	Percentage	Total, + <i>PTEN</i> mutation	Percentage
<i>n</i> , with colonoscopy	5	10	10	10	67	5	107		88	
<i>PTEN</i> mutation	4	10	NR	5	67	2	88	82%	88	100%
Age (yr), mean	45.8	31.7	37	48	36.4	34	37.4		36.9	
# of colonoscopies, mean	4.2	2.4	3.1	2	NR	NR	2.7		2.9	
Patients with colon polyps	5	8	10	9	62	5	99	92.5%	81	92%
> 50 polyps	1	NR	8	7	NR	NR	16	64%	5	55.6%
Pancolonic location	3	7	7	8	NR	NR	25	71.4%	14	73.7%
Left-sided location	2	1	NR	1	NR	NR	4	16%	3	15.8%
<i>n</i> , with colonic pathology	4	8	10	11	56	5	94		75	
Adenocarcinoma	0	1	0	2	9	0	12	12.8%	12	16%
Adenoma	2	3	10	6	16	1	38	40.4%	24	32%
Ganglioneuroma	1	3	5	6	16	0	31	33%	23	30.7%
Hamartoma	0	5	6	7	18	0	36	38.3%	27	36%
Hyperplastic	2	8	0	4	27	0	41	43.6%	39	52%
Inflammatory	0	0	0	7	11	5	23	24.5%	18	24%
Juvenile	1	2	0	2	0	0	5	5.3%	5	6.7%
Lymphoid hyperplasia/polyp	0	0	0	0	4	1	5	5.3%	5	6.7%
Sessile serrated polyp	0	0	0	0	2	0	2	2.1%	2	2.7%
1 polyp type	2	1	NR	2	29	3	37	44%	32	42.7%
2 polyp types	2	4	NR	2	16	2	26	31%	25	33.3%
≥ 3 polyp types	0	3	NR	7	9	0	19	22.6%	16	21.3%

NR: Not reported.

ba syndrome and the composite PHTS since the earliest reports of the disease, but the prevalence of findings and the pathologic diversity was underestimated due to lack of routine endoscopy and polypectomy. Current research is changing the perception of the GI polyposis prevalence, pathology and most importantly the risk of malignancy.

Our cohort included 5 patients with PHTS that underwent colonoscopy. We noted a 100% prevalence of colonic polyps, which corresponds with the high prevalence of colonic polyposis that has been reported recently. Although polypectomy was not performed on all patients, we found a higher incidence of adenomatous and hyperplastic polyps and relatively few of the classically associated hamartomatous polyps, which were only reported in a single patient. This patient was noted to have diffuse colonic ganglioneuromatous polyps with an isolated juvenile polyp found on gross pathology specimen after colectomy.

Our systematic review of case series published after the establishment of Cowden syndrome diagnostic criteria and the widespread use of endoscopy also supports the high rate of endoscopic findings and polyposis in PHTS. Colonic polyps were found in 92.5% of patients, with similar rates when only *PTEN* mutation positive patients were considered. In addition, a variety of polyp histologies were reported, with hyperplastic, adenomatous, hamartomatous, ganglioneuromatous and inflammatory polyps all being common in the colon. Importantly, the majority of patients with colon polyp pathology interpretation were found to have 2 or more histologic types.

Given the prevalence of multiple polyp histologies-including hyperplastic polyps, adenomas and hamartomas-we suggest that PHTS be reclassified as a mixed poly-

posis syndrome rather than a hamartomatous polyposis syndrome. If hamartomatous polyps were relied upon to suggest PHTS as a possible diagnosis, many patients in our series would have gone undetected. In further support of this nomenclature shift, Sweet *et al.*^[20] have previously investigated patients with unexplained polyposis syndromes consisting of hyperplastic and adenomatous polyps without hamartomas and detected *PTEN* mutations in 2 (9%) patients from a cohort of 23^[20]. Thus, we believe the current classification is misleading and investigation for PHTS should not depend on the presence of hamartomatous GI polyps.

There has been a paradigm shift regarding the risk of colorectal cancer in PHTS. Recent work has shown an increased risk of colorectal cancer in this population, with a 9%-18% prevalence of colorectal cancer and standardized incidence rate of 10.3 (95%CI: 5.6-17.4) reported^[18,13,14,21]. There are also reports of young onset colorectal cancer in this population, with Kersseboom *et al.*^[22] reporting diagnoses at 28 and 39 years of age. This has resulted in the National Comprehensive Cancer Network changing their recommendations to include considering colonoscopy starting at age 35 years, then every 5-10 years or more frequently if patient is symptomatic or polyps found^[15].

Based on our systematic review, we found a 11.2% prevalence of colorectal cancer in PHTS patients undergoing GI work-up and 13.6% in *PTEN* mutation positive patients. The mean age of colorectal cancer diagnosis was 46.7, with the earliest found at age 35. Based on this, it is reasonable to start colonic surveillance at either age 35 or 10 years younger than the earliest colorectal cancer diagnosis in a first-degree relative, whichever is sooner.

We then recommend proceeding with further colonic surveillance based on the findings, with colonoscopy every 1-2 years if multiple polyps and/or adenomatous polyps are present or every 3-5 years if either sparse, non-adenomatous polyps or no polyps are present. The use of additional techniques such as narrow-band imaging^[23], probe-based confocal laser endomicroscopy^[24] or other emerging technologies to help discern polyp histology in real time and direct polypectomy efforts towards higher risk lesions should be considered if the technology and expertise is available.

Unfortunately, minimal data on the clinical outcomes resulting from the GI polyposis in this population are available. The mean number of colonoscopies per patient based on the systematic review was 2.7, although the time course these took place over is unknown. In our cohort, 1 (20%) that received a colonoscopy underwent colectomy due to concern for future malignant potential. In the Mayo Clinic cohort, 5 (38%) patients underwent colectomy due to dysplastic colon lesions^[16]. The other case series do not report clinical outcomes. When initiating colonic surveillance, it is important to discuss possible outcomes with patients including the need for repeated procedures and the possibility of colectomy if colorectal cancer, high risk lesions or multiple polyps are present. Further investigation is needed in this area to clarify the optimal surveillance protocol and to allow for adequate counseling and treatment of PHTS patients with GI polyposis.

Several areas of caution should be noted when interpreting this data. Due to the method of subject accrual being based on review of outside records in the Heald *et al.*^[14] study, we cannot definitively rule out the possibility that some patients from other cohorts may be included in their cohort. Ascertainment bias should also be taken into account, as PHTS patients without GI manifestations may be less likely to undergo endoscopic evaluation and may be under-represented. Thus, neither our data nor that in the published literature can be used to determine the true prevalence of GI abnormalities in PHTS. Future work in this area, aided by the new recommendations favoring colorectal cancer surveillance, should help clarify this and confirm the current data.

In summary, PHTS has a high prevalence of colonic polyposis. The classically associated hamartomatous polyps cannot be relied on to suggest the diagnosis, and patients with multiple polyp histologies need to be examined further for PHTS. An increased risk of colon cancer is now reported and surveillance with colonoscopy is indicated. We recommend starting at age 35 or 10 years younger than the earliest colorectal cancer diagnosis in a first-degree relative with future surveillance intervals based on the results.

COMMENTS

Background

The phosphatase and tensin homolog on chromosome ten (*PTEN*) gene is a tumor suppressor that regulates cell growth. Germline mutations of this gene leads to Cowden syndrome and other disorders that are now collectively known

as the *PTEN* hamartoma tumor syndrome. Gastrointestinal polyposis is a known manifestation of the disorder since the initial reports, but were thought to be benign hamartomas without malignant potential. Recent case series have indicated mixed polyp histology and an increased colon cancer risk.

Research frontiers

Continued investigation into the malignant potential and clinical outcomes of colonic polyposis in the *PTEN* hamartoma tumor syndrome, including cost effectiveness of colon cancer screening and surveillance.

Innovations and breakthroughs

The authors report findings from our *PTEN* hamartoma tumor syndrome patients undergoing colonoscopy which show all with colon polyps and 40% with multiple polyp histologies. They detail the clinical outcomes of these polyps, including a patient that received colectomy. They also performed a systematic review of the modern literature focusing on gastrointestinal manifestations; this revealed 92.5% with colon polyps and a majority of patients with multiple polyp histologies. The systematic review also supports an increased risk of colon cancer.

Applications

PTEN hamartoma tumor syndrome should be considered a mixed polyposis syndrome and this diagnosis should be considered in patients with multiple polyp histologies. The authors' findings also support an increased risk of colon cancer and we recommend colonoscopy for colorectal cancer surveillance beginning at either age 35 or 10 years younger than the earliest colorectal cancer diagnosis in a first-degree relative, whichever is sooner. Future research should include clinical outcomes.

Peer review

In this paper, the authors analysed and reviewed patient data from their institute and literature to identify the connection between gastrointestinal abnormalities (in particular colon lesions/cancer) and *PTEN* hamartoma tumor syndrome (PHTS) to make recommendation for future clinical examination of patients. The study was well organized and clearly set up. The authors reported that PHTS had a high prevalence of colonic polyposis. It will be interesting to know the connection of the high prevalence of colonic polyposis in PHTS patients to the risk of gastrointestinal (colon in particular) cancers.

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P- Reviewers: He H, Pichler M S- Editor: Qi Y
L- Editor: A E- Editor: Wang CH





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ISSN 1007-9327



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