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ARTICLE

Spectrum of gastrointestinal tract pathology in a multicenter cohort of 43 Cowden syndrome patients

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Abstract

Most patients with Cowden syndrome have lesions in the gastrointestinal tract, characterized by multiple polyps of various histologic types in the large bowel, polyps in the upper gastrointestinal tract, and esophageal glycogenic acanthosis. However, pathologists are often unaware of the distinctive polyposis phenotype of Cowden syndrome. In this multicenter study, we report the spectrum of gastrointestinal manifestations in a series of 43 Cowden syndrome patients who had at least one endoscopy. The median age at the first endoscopy was 46 years and 58% were women. In 24 of 29 (83%) tested patients, a pathogenic germline mutation in PTEN was identified. The histology from 199 endoscopy procedures (67 upper gastrointestinal endoscopy and 132 colonoscopies) was reviewed. Hamartomatous polyps of the large bowel were the most common lesions, present in 85% of patients. Hamartomatous polyps showed varied histology, including lymphoid aggregates in 55% of patients, a lipomatous component in 52%, a ganglioneuromatous component in 52%, and a fibrous-rich component in 14%. Polyps with at least two different stromal components were found in 55% of patients. Inflammatory polyps were present in 21% of patients. Conventional adenomas and serrated polyps were identified in 48% and 62% of patients, respectively. In the upper gastrointestinal tract, the most common lesions were esophageal glycogenic acanthosis (37%), gastric hamartomatous polyps (47%), and duodenal hamartomatous polyps (20%). All patients with glycogenic acanthosis who had a colonoscopy had hamartomatous polyps of the large bowel. In five patients, the diagnosis of Cowden syndrome was established after the pathology report raised suspicion for the diagnosis. Pathologists who are aware of the characteristic admixture of lesions in Cowden syndrome can play an essential role in recommending referral to genetic counseling and gene testing. Early diagnosis of Cowden syndrome is important, as these patients and their relatives are at increased risk for developing multiple cancers.

Introduction

Cowden syndrome is an autosomal dominant multisystem disorder characterized by the development of multiple hamartomas in various organs and an increased risk of

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cancer. It is the most common condition within the group of *PTEN* hamartoma tumor syndrome caused by germline mutations in *PTEN*, a tumor suppressor gene located on chromosome 10q23.3 [1]. The protein product of the gene antagonizes the phosphatidylinositol 3-kinase and the mitogen-activated protein kinase signaling pathways, both involved in cell growth regulation [2–4]. The clinical diagnosis of Cowden syndrome is based on criteria from the National Comprehensive Cancer Network and the International Cowden Syndrome Consortium operational diagnostic criteria [5–7]. Approximately 85% of individuals meeting the clinical criteria are found to carry a pathogenic germline mutation in *PTEN* [3, 8].

The most common clinical manifestations of Cowden syndrome are mucocutaneous lesions, gastrointestinal hamartomas, and macrocephaly. In one of the first descriptions of Cowden syndrome-associated gastrointestinal lesions, Heald et al. reported a high prevalence of multiple polyps in the large bowel, ileum, duodenum, and stomach in a series of 67 *PTEN* mutation carriers [9]. Colorectal polyps were usually small (<10 mm) sessile lesions of various histologic types, comprising hamartomatous polyps, hyperplastic polyps, ganglioneuromas, and adenomas. Glycogenic acanthosis was another common benign lesion of the esophagus. Subsequent studies from small numbers of Cowden syndrome patients reported a high prevalence of polyps in the gastrointestinal tract in >90% of patients and a small increased risk of colorectal cancer [10–14].

The prevalence of Cowden syndrome is estimated at 1 in 200,000, although this figure is likely an underestimate due to underrecognition by the medical community and difficulties in making the diagnosis of a syndrome often involving multiple medical specialties [15]. Pathologists are often unaware of the characteristics of Cowden syndrome polyps and the associated conditions. However, the particular combination of polyp histologic types can be a clue to raise the possibility of Cowden syndrome and recommend genetic counseling. Early diagnosis is important to commence screening for the associated malignancies, including breast cancer, thyroid cancer, and endometrial cancer. In this multicenter study, we investigated the spectrum of histologic findings in 43 patients with a clinical diagnosis of Cowden syndrome, who underwent a total of 199 endoscopy procedures.

Materials and methods

Study cohort

Patients were recruited retrospectively from five institutions in two countries: Pathology Queensland, Sullivan and Nicolaides Pathology, and Envoi Specialist Pathologists in Brisbane, QLD, Australia; Massachusetts General Hospital in Boston, MA, USA; and Department of Pathology, University of Chicago, IL, USA. This study was approved by the Human Research Ethics Committees at each location.

The pathology and genetic databases were searched for the terms "Cowden", "Cowdens", "Cowden's", and "PTEN" for the years 1993–2015. Patients with a clinical diagnosis of Cowden syndrome or with a pathogenic germline *PTEN* mutation who had at least one upper gastrointestinal endoscopy and/or colonoscopy with histology were included in the study.

The following clinical features were recorded from endoscopy reports and patient charts were available: age, sex, clinical indication for endoscopy, *PTEN* mutation status, family history of Cowden syndrome, number of polyps in the gastrointestinal tract, and number of endoscopy procedures. Age at diagnosis was the patient age at the time of the first upper gastrointestinal endoscopy and/or first colonoscopy. Estimates of colorectal polyp count were obtained from the colonoscopy reports. When no specific count was recorded in the report or when a non-quantitative term was used ("multiple", "many", or "several"), the polyp number was the number of biopsy fragments showing any type of polyp. The following clinical manifestations of Cowden syndrome were recorded: macrocephaly, Lhermitte–Duclos disease, autism, mental retardation, mucocutaneous lesions, macular pigmentation of the glans penis, lipoma, fibroma, breast cancer, fibrocystic breast disease, follicular thyroid cancer, other thyroid lesions, endometrial cancer, and genitourinary tumors.

Histology review

The hematoxylin and eosin-stained sections of the gastrointestinal pathology lesions were reviewed by two pathologists at each site. Glycogenic acanthosis of the esophagus was defined as an endoscopic white lesion showing mild squamous hyperplasia and hypertrophic superficial cells filled with glycogen. Polyps were categorized into hamartomatous polyp, serrated polyp (hyperplastic polyp and sessile serrated polyp), conventional adenoma, and inflammatory polyp. In the stomach, hamartomatous/inflammatory polyps were characterized by foveolar hyperplasia and inflamed lamina propria with increased number of myofibroblasts. Intestinal hamartomatous polyps were defined as polypoid mucosal lesions containing various types of stromal components and nondysplastic crypts with some degree of architectural distortion, including crypt elongation, bifurcation of crypts, or crypt shortening. The stromal component always expanded the lamina propria. Colonic polyps resembling juvenile polyps with inflamed lamina propria and dilated crypts were included in the total

hamartomatous polyp count. For each polyp, the presence of a neuromatous or ganglioneuromatous component, mucosal lipomatous component, lymphoid aggregates, and a fibrous-rich component was documented. The fibrous rich stroma was characterized by bland spindle cell proliferation in the lamina propria and the superficial submucosa with some encasement of crypts. In some instances, this stroma displayed a whorling pattern of collagen reminiscent of collagenous fibroma of the skin. Some polyps were immunostained for S-100 and CD34 at the time of initial diagnosis. These stains were used to confirm a neuromatous component with partial S-100 positivity in spindle cells and to highlight the pattern of spindle cell proliferation in fibrous-rich hamartomatous polyps. When more than one of these components was present in the same polyp, all were counted as present. Colonic polyps with inflamed lamina propria but without significant stromal proliferation were diagnosed as inflammatory polyps. Additional relevant pathological diagnoses were recorded when encountered.

Statistical analysis

Patient age is reported as median and range. The number of endoscopy procedures and of polyps is reported as median and range. Categorical variables were compared using Fisher's exact test. Continuous variables were compared using Mann–Whitney *U* test. A P-value < 0.05 was considered significant.

Results

Clinical characteristics

The clinical features are summarized in Table 1 and Supplementary Table 1. The study cohort consisted of 43 patients from 42 families with a clinical diagnosis of Cowden syndrome. A pathogenic germline mutation in *PTEN* was identified in 24 of 29 (83%) tested patients. The median age at the first endoscopy was 46 years (range 15–67) and 25 (58%) patients were women. Seventeen patients were aged 50 years or older. There were 18 patients from Brisbane, 13 from Chicago, and 12 from Boston. Clinical information on Cowden syndrome-associated conditions was available for 28 patients. The most common clinical manifestations included macrocephaly (36%), mucocutaneous lesions (21%), breast cancer (56% females), and thyroid lesions other than follicular carcinoma (64%).

Clinical indication for endoscopy was screening in known Cowden syndrome for most patients. For five patients, the possibility of Cowden syndrome was first suggested by the pathology report of endoscopic biopsies and confirmed by identification of a pathogenic *PTEN* mutation. One 56-year-old male had a colonoscopy for polyp surveillance, showing four hamartomatous polyps with lymphoid aggregates. A 23-year-old female undergoing upper and lower endoscopy for irritable bowel syndrome was found to have one gastric hyperplastic polyp and 20 hamartomatous polyps of the colon, with admixed adipose tissue, lymphoid aggregates, and ganglioneuromatous components. A 41-year-old female was investigated for family history of cancer and was diagnosed with glycogenic acanthosis, 13 colonic hamartomatous polyps with lymphoid aggregates and mucosal lipomatous components, and three serrated polyps. A 35-year-old male had a colonoscopy for unknown indication reporting >30 colorectal polyps; histologically, 14 hamartomatous polyps were identified with lipomatous component, lymphoid aggregates, and ganglioneuromatous components. A 15-year-old female underwent an upper and lower endoscopy for elevated fecal calprotectin and possible familial adenomatous polyposis in her mother and grandmother. One duodenal hamartoma, eight colonic hamartomas with ganglioneuromatous components and lymphoid aggregates, and six colonic inflammatory polyps were identified. Pathology from a colonoscopy performed on her mother 6 years earlier at 46 years of age was reviewed and showed four hamartomatous polyps and one serrated polyp in the large bowel.

Table 1 Clinical features of 43 patients with a clinical diagnosis of Cowden syndrome, who had at least one endoscopy procedure

Clinical feature	Number (%)
Age, median (range)	46 years (15–67)
Female	25 (58%)
Germline testing for *PTEN* mutation	25 (61%)
Pathogenic *PTEN* mutation	24/29 (83%)
Family history of Cowden syndrome	10/28 (36%)
Macrocephaly	10/28 (36%)
Lhermitte–Duclos disease	1/28 (4%)
Autism spectrum disorder	0/28 (0%)
Mental retardation	1/28 (4%)
Pathognomonic mucocutaneous lesions	6/28 (21%)
Macular pigmentation of the glans penis	3/12 (25%) males
Lipomas	6/28 (21%)
Fibromas	4/28 (14%)
Breast cancer	9/16 (56%) females
Fibrocystic breast disease	6/16 (37%) females
Follicular thyroid cancer	2/28 (7%)
Other thyroid lesions	18/28 (64%)
Endometrial cancer	3/16 (19%) females
Genitourinary tumours	3/28 (11%)

Gastrointestinal pathology

All but one patient (98%) had at least one colonoscopy, 30 (70%) had at least one upper gastrointestinal endoscopy, and 29 (67%) had both procedures. Information on follow-up endoscopy procedures was available for 32 patients. A median of three procedures per patient were performed during a median follow-up of 6 years (range 1–26). The total number of upper gastrointestinal endoscopies was 1 for 14 (33%) patients, 2 for 5 (12%) patients, 3 for 5 (12%) patients, 4 for 3 (7%) patients, 5 for 2 (5%) patients, and 6 for 1 (2%) patient. The total number of colonoscopies was 1 for 10 (23%) patients, 2 for 6 (14%) patients, 3 for 10 (23%) patients, 4 for 8 (19%) patients, 5 for 4 (9%) patients, 6 for 1 (2%) patient, 7 for 2 (5%) patients, and 8 for 1 (2%) patient. The histology from a total of 199 endoscopy procedures (67 upper gastrointestinal endoscopy and 132 colonoscopies) was available for review.

Histologic and immunohistochemical findings in the large bowel and the terminal ileum

A total of 710 colorectal polyps were documented, comprising 527 hamartomatous polyps, 52 serrated polyps, 101 conventional adenomas, and 30 inflammatory polyps. Only one (2%) patient had a hamartomatous polyp in the terminal ileum (Table 2). The median total number of colorectal polyps was 4.5 (range 1–20) at index colonoscopy and 13 (range 1–63) on multiple colonoscopies. Colorectal hamartomatous polyps were identified in 36 (85%) patients with a maximum count of 58 polyps in a patient who had four colonoscopies. Among the five patients without any colorectal hamartomatous polyps, one had ten inflammatory polyps associated with nine conventional adenomas and one serrated polyp, while the other four patients had serrated polyps only or in combination with conventional adenomas.

The most common stromal components in hamartomatous polyps comprised lymphoid aggregates, mucosal lipoma, and ganglioneuroma, each in approximately half of patients (Fig. 1). Colorectal hamartomatous polyps with at least two different stromal components were present in 22 (55%) patients (Table 3). In 12 polyps with a predominant spindle cell component, immunostains for S-100 and CD34 sections were reviewed, showing seven fibrous-rich hamartomatous polyps with CD34 positivity in spindle cells, two polyps with partial S-100 positivity in spindle cells, and two polyps with both S-100 and CD34 positivity in spindle cells. S-100 immunohistochemistry highlighted the neuromatous component in some hamartomatous polyps, when no ganglion cells were seen. The CD34 immunostain demonstrated the whorling pattern of spindle cells around colonic crypts (Fig. 2).

Serrated polyps were present in 26 (62%) patients and conventional adenoma in 20 (48%) patients. The prevalence of serrated polyps and conventional adenomas at index colonoscopy was 16 (38%) and 15 (36%), respectively. In the 26 patients younger than 50 years of age, the prevalence of serrated polyps and conventional adenomas was 11 (42%) and 8 (31%), respectively, at the index colonoscopy. All serrated polyps were hyperplastic polyps or sessile serrated polyps. All conventional adenomas were tubular or tubulovillous adenoma with low-grade dysplasia. Hamartomatous polyps were associated with serrated polyps in 20 (48%) patients and with conventional adenoma in 18 (43%) patients. All ten patients with glycogenic acanthosis of the esophagus who also had a colonoscopy had colorectal hamartomatous polyps.

Histologic findings in the upper gastrointestinal tract

The most common upper gastrointestinal tract manifestations present in at least one endoscopy procedure were glycogenic acanthosis in the esophagus identified in 11 (37%) patients and gastric hamartomatous/inflammatory polyps in 14 (47%) patients (Table 4) (Fig. 3). Less frequent lesions included high-grade squamous dysplasia of the esophagus ($n = 1$), squamous papilloma of the esophagus ($n = 1$), gastric fundic gland polyp ($n = 6$), gastric adenoma ($n = 1$), duodenal hamartomatous/inflammatory polyp ($n = 6$), duodenal gastric heterotopia ($n = 5$), duodenitis ($n = 6$), duodenal submucosal lipoma ($n = 1$), and ganglioneuroma ($n = 1$).

Correlation between histologic findings and clinical features

Clinical features (patient age, sex, and the presence of *PTEN* mutation) were compared with the presence of glycogenic acanthosis, gastric polyp, and the presence and the number of colorectal polyps at index endoscopy and at any endoscopy during follow-up. *PTEN* mutation was associated with the presence of a hamartomatous polyp in at least one colonoscopy (100% in patients with *PTEN* mutation vs. 60% in patients without *PTEN* mutation, $P = 0.03$) and with the presence of a lymphoid hyperplasia component (61% in patients with *PTEN* mutation vs. 0% in patients without *PTEN* mutation, $P = 0.04$). No other significant association was identified.

Discussion

Since the earliest descriptions, polyposis of the gastrointestinal tract has been recognized as one of the most

Table 2 Histologic findings in the terminal ileum and large bowel from 42 patients who had at least one colonoscopy

Histologic findings	Present at index colonoscopy	Polyp number at index colonoscopy (median, range)	Present in at least in one colonoscopy	Cumulative polyp number (median, range)
Terminal ileum				
Hamartoma	1 (2%)	1	1 (2%)	1
Ganglioneuroma	1 (2%)	1	1 (2%)	1
Large bowel				
Hamartomatous polyp	34 (81%)	3 (1–20)	36 (85%)	12 (1–58)
Lymphoid aggregates	18 (43%)	2 (1–11)	24 (57%)	2.5 (1–15)
Lipomatous component	12 (29%)	1 (1–4)	22 (52%)	2 (1–10)
Ganglioneuromatous component	11 (26%)	1 (1–4)	22 (52%)	2 (1–18)
Fibrous-rich component	2 (5%)	1	6 (14%)	3 (2–9)
Inflammatory polyp	5 (12%)	1 (1–2)	9 (21%)	1.5 (1–10)
Serrated polyp	16 (38%)	1 (1–4)	26 (62%)	2 (1–5)
Conventional adenoma	15 (36%)	2 (1–13)	20 (48%)	3.5 (1–18)
All types of polyps	42 (100%)	4.5 (1–20)	42 (100%)	13 (1–63)

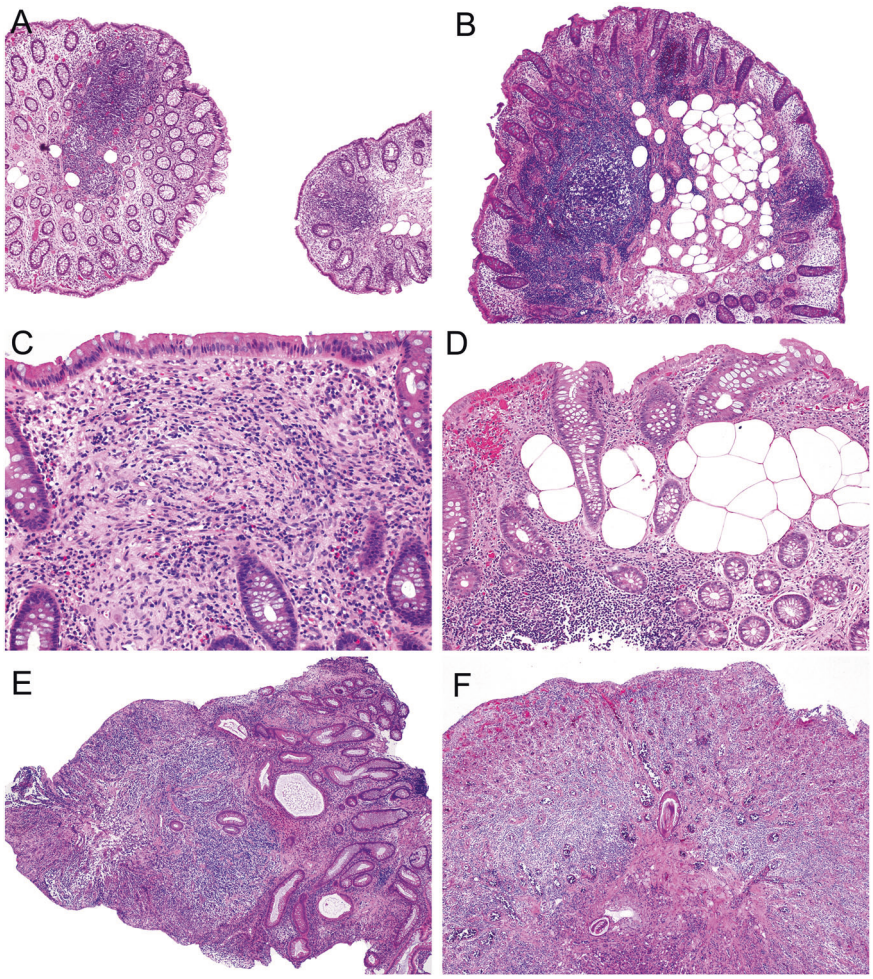

Fig. 1 Examples of colorectal polyps. Two small polyps with lymphoid aggregates and a few adipocytes in the lamina propria (**a**), a hamartomatous polyp with a large lymphoid aggregate and a lipomatous component (**b**), a hamartomatous polyp with a predominant ganglioneuromatous component (**c**), a hamartomatous polyp with a predominant mucosal lipomatous component (**d**), an inflammatory polyp with distorted crypts and a cap of a mixed inflammatory infiltrate (**e**), and an inflammatory polyp consisting essentially of granulation tissue (**f**)

common manifestations of Cowden syndrome, with a prevalence of >90% of patients who underwent an endoscopy [9, 11, 13, 16, 17]. However, gastrointestinal pathologists are often unaware of the distinctive phenotype of Cowden syndrome and may miss the opportunity to prompt consideration of this diagnosis when reporting such lesions. To further explore the gastrointestinal phenotype of this underrecognized condition, we report the histologic findings from a large cohort of Cowden syndrome patients who had at least one endoscopy. The total polyp burden in the large bowel was variable, with a median of 13 polyps of any type and up to 63 histologically confirmed polyps. Hamartomatous polyp was the most common lesion present in 85% of patients and the type of polyp with the highest count per patient. Inflammatory polyps were present in 21% patients and often multiple. They resemble inflammatory polyps secondary to mucosal prolapse. We included juvenile-type polyps, ganglioneuromas, lymphoid aggregates, and lipomas in an overarching group of hamartomatous polyps, as these components are often mixed in a single lesion. This likely explains the higher prevalence of hamartomatous polyps in our series, compared with previous studies [9–13, 17]. In 55% of patients, a combination of two or more stromal components was present, confirming the characteristic diversity of hamartomatous polyps in Cowden syndrome. It is this diversity of stromal components that is the most important phenotypic marker of gastrointestinal tract Cowden syndrome.

Table 3 Combination of various histologic findings

Combined colonoscopy findings ($n = 42$)	
Hamartomatous polyps with ≥2 stromal components	23 (55%)
Hamartomatous polyps with ≥3 stromal components	16 (38%)
Hamartomatous polyp and conventional adenoma	18 (43%)
Hamartomatous polyp and serrated polyp	20 (48%)
Hamartomatous polyp and conventional adenoma and serrated polyp	13 (31%)
Combined upper gastrointestinal tract endoscopy and colonoscopy findings ($n = 29$)	
Glycogenic acanthosis and colorectal hamartomatous polyp	10 (34%)
Gastric and colorectal hamartomatous polyp	11 (38%)

Mucosal lipomas of the large bowel were identified in 52% patients. In a series of 25 patients with mucosal lipomas, Caliskan et al. reported that five of them (20%) had a confirmed Cowden syndrome, suggesting that these lesions are an important diagnostic feature of this disorder [10]. Submucosal lipoma is less suggestive of Cowden syndrome when isolated. As in our series, Cowden syndrome-associated mucosal lipomas were observed in combination with other hamartomatous components, most commonly lymphoid aggregates and spindle cell proliferation. While mucosal lipomas are an important clue to the diagnosis of Cowden syndrome, our results indicate that they are present in only half of patients.

The spindle cells in Cowden syndrome hamartomatous polyps are bland, usually associated with other components. S-100 immunohistochemistry can be helpful to confirm a neuromatous origin, when ganglion cells are not prominent. A CD34-positive spindle cell proliferation with concentric pattern around crosscut crypts associated with a dense fibrotic stroma was the characteristic feature of a subgroup

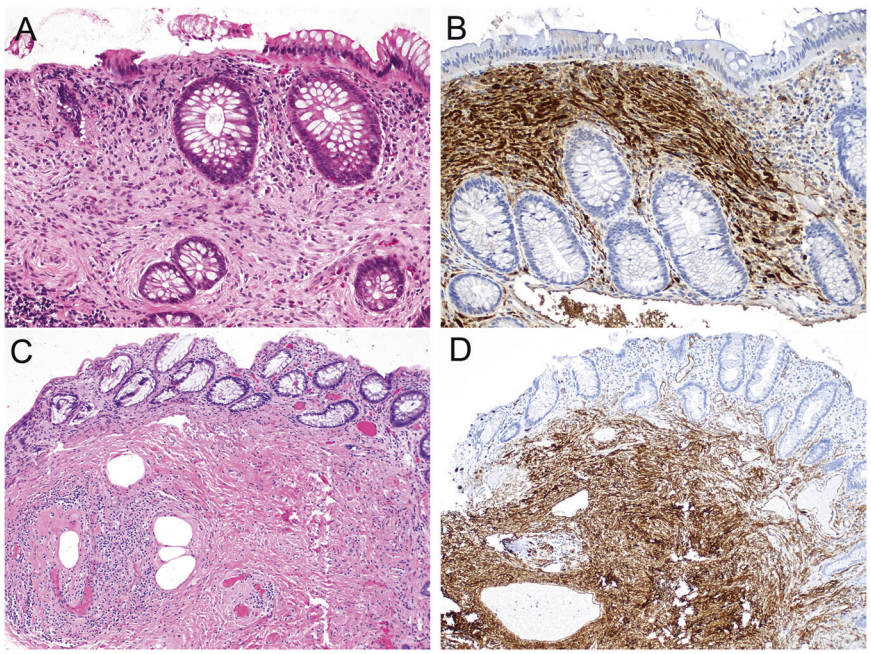

Fig. 2 A hamartomatous polyp of the colon with a neuromatous component and positivity with S-100 (**a**, **b**). A fibrous-rich hamartomatous polyp of the colon with positivity of spindle cells with CD34 (**c**, **d**)

of polyps, referred to as fibrous-rich hamartomatous polyp. The significance of CD34 positivity in this context is unclear. We did not perform immunostaining on other types of hamartomatous polyps to address the specificity of CD34 positivity in Cowden syndrome.

Previous studies described a 9% increased risk of colorectal cancer in Cowden syndrome patients [14]. Current surveillance guidelines recommend screening colonoscopy starting at 40 years every 2 years [6, 14]. No colorectal cancer was identified in our series at index colonoscopy or on follow-up. However, serrated polyps and conventional adenomas were found overall in 62% and 48% of patients and at index colonoscopy in 38% and 36%, respectively. Furthermore, in patients <50 years of age, the prevalence of serrated polyps and conventional adenomas was 42% and 31%, respectively, at the index colonoscopy. This prevalence of conventional adenoma, a likely precursor of most colorectal cancer in Cowden syndrome patients, is higher than expected from an average-risk population in the age range of our cohort [18]. This supports that conventional adenoma is part of the phenotype of Cowden syndrome. In nearly half of patients, hamartomatous polyps were associated with either serrated polyps or conventional adenomas. These findings further highlight that hamartomatous polyps are not only of varied histology but are also commonly associated with conventional adenomas and serrated polyps.

Table 4 Histologic findings in the upper gastrointestinal tract from 30 patients who had at least one endoscopy

Histologic findings	Present at index endoscopy	Present in at least in one endoscopy
Esophagus		
Glycogenic acanthosis	9 (30%)	11 (37%)
Squamous dysplasia (high grade)	0	1 (3%)
Squamous papilloma	1 (3%)	1 (3%)
Stomach		
Hamartomatous/ inflammatory polyp	12 (40%)	14 (47%)
Fundic gland polyp	4 (13%)	6 (20%)
Adenoma	1 (3%)	1 (3%)
Duodenum		
Hamartomatous polyp	2 (7%)	6 (20%)
Gastric heterotopia	2 (7%)	5 (17%)
Duodenitis	4 (13%)	6 (20%)
Submucosal lipoma	1 (3%)	1 (3%)
Ganglioneuroma	1 (3%)	1 (3%)

In the upper gastrointestinal tract, the most common lesions in our study were glycogenic acanthosis of the esophagus (37%), gastric hamartomatous polyps (47%), and duodenal hamartomatous polyps (20%). Glycogenic acanthosis of the esophagus is particularly characteristic of Cowden syndrome, reported in up to 80% of patients undergoing endoscopic surveillance [15, 19, 20]. It has been suggested that extensive glycogenic acanthosis of the esophagus associated with benign gastrointestinal polyps is pathognomonic for Cowden disease [20]. In our study, all patients with glycogenic acanthosis who had a colonoscopy had hamartomatous polyps in the large bowel. However, a combination of glycogenic acanthosis and colorectal

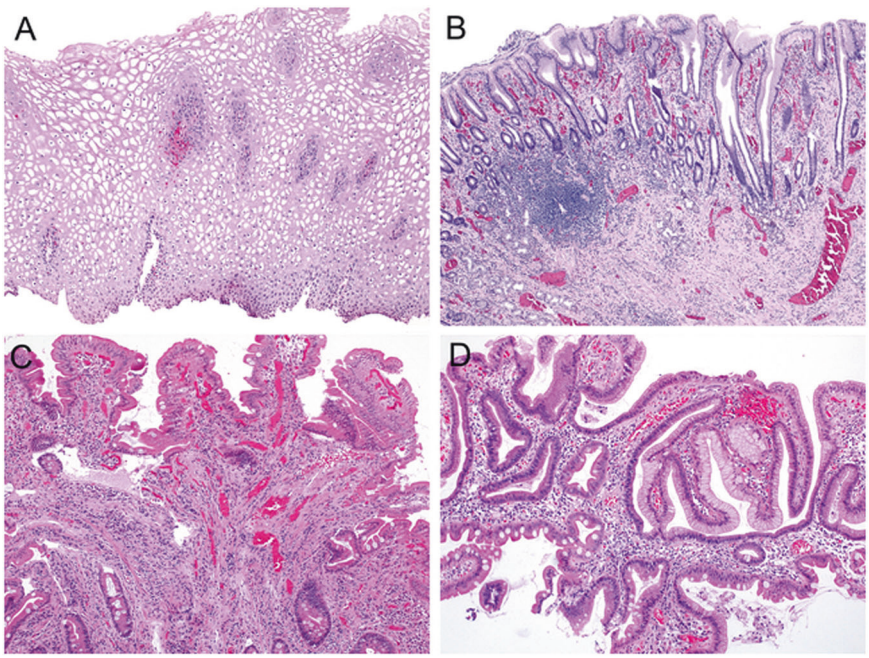

Fig. 3 Examples of lesions in the upper gastrointestinal tract. Glycogenic acanthosis of the esophagus (**a**), a gastric hamartomatous polyp (**b**), and hamartomatous polyps in the duodenum (**c**, **d**)

hamartomatous polyp was found in only 34% of patients. Hamartomatous polyps in the upper gastrointestinal tract do not have any specific histologic features that distinguish them from sporadic lesions. In the stomach, they resemble sporadic hyperplastic/inflammatory polyps. In the duodenum, hamartomatous polyps are often small and may look like nodular duodenitis. Hamartomatous polyposis syndromes cannot be distinguished based on the histology of gastric and duodenal polyps [21]. One patient was diagnosed with high-grade squamous dysplasia of the esophagus, a finding not reported in previous studies. It is unclear whether this is coincidental or part of the spectrum of Cowden syndrome.

An important aspect of our study is that Cowden syndrome was diagnosed in five patients after the pathology report of colorectal polyps suggested the diagnosis. These examples illustrate how pathologists who are aware of the characteristic admixture of polyp histology in Cowden syndrome can suggest the diagnosis. Colonic polyps can be the initial finding that leads to the diagnosis. In a previous report of ten Cowden syndrome patients who had a colonoscopy, the diagnosis had been established from the findings of numerous polyps for four patients [16]. Additional clues to pathologists may come from previous reports of other lesions associated with Cowden syndrome (trichilemmomas, breast cancer, endometrial cancer, and thyroid follicular cancer). In these instances, pathologists should alert clinicians about the possibility of Cowden syndrome in order to pursue genetic counseling. Early diagnosis of Cowden syndrome is essential to screen these patients for breast cancer (estimated risk 25–85%), thyroid cancer (35% risk), endometrial cancer (19–28% risk), and renal cell carcinoma (34% risk) [6, 14].

This study has a number of limitations. It is a retrospective study from multiple centers with incomplete clinical information for 15 (35%) patients. Because all patients were selected based on availability of histology specimens, we do not have information on patients with normal endoscopy or for whom no specimen was submitted for histology. The polyp count is based on histology review and is likely an underestimate of the actual polyp counts from colonoscopy. When available, endoscopy reports often mention the presence of multiple polyps with sampling of only a few (probably the larger ones) for histology.

In conclusion, we report that Cowden syndrome patients who underwent an endoscopy have a characteristic polyp phenotype in the gastrointestinal tract that can lead to the diagnosis. Pathologists who are aware of the typical admixture of hamartomatous polyps and the related conditions can play an important role in suggesting the diagnosis of Cowden syndrome. Referral to genetic counseling and gene testing should be advised in the appropriate setting to confirm the diagnosis and commence early cancer surveillance for the proband and affected siblings.

Compliance with ethical standards

Conflict of interest This project was supported by funding from the Pathology Queensland Study, Education and Research Committee (SERC). The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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