Endoscopic and Pathological Characteristics of Cronkhite–Canada Syndrome: A Retrospective Analysis of 76 Cases

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ABSTRACT

Background: *Cronkhite–Canada syndrome (CCS) is a disease of unknown etiology characterized by the presence of multiple gastrointestinal polyps, chronic diarrhea, loss of appetite, alopecia, onychodystrophy, and cutaneous hyperpigmentation. CCS is a rare disease with an incidence rate of 1 per million. Clinicians are not aware of this disease, and the discovery of gastrointestinal polyps is often a starting point for the diagnosis of this disease. By analyzing the endoscopic and pathological characteristics of CCS, this study aims to deepen our understanding of gastrointestinal polyposis and facilitate early diagnosis of CCS.*

Methods: *We screened databases, including the Chinese Biomedical Literature Database (CBM Web), the China Academic Journals Full-text Database (CJFD), and PubMed for CCS cases reported from January 2010 to January 2020, and conducted a retrospective analysis of endoscopic and pathological characteristics of these cases.*

Results: *The endoscopic data of the 76 retrieved cases revealed that CCS is gastrointestinal polyposis with the intensive and confluent distribution. The greater the number of polyps and the higher their distribution, the brighter their color. A pathological assessment revealed that both gastric polyps and intestinal polyps are mainly juvenile hamartomatous polyps and have a high malignant transformation rate. Interstitial edema, eosinophil infiltration, and cystic dilation of glands are common features of CCS polyps, distinguishing them from other gastrointestinal polyposis syndromes.*

Conclusion: *CCS is a polyp disease different from other gastrointestinal polyposis. Analysis of its endoscopic and pathological characteristics can contribute to the understanding and early diagnosis of the disease.*

Keywords: *Cronkhite–Canada syndrome (CCS), gastrointestinal polyp, hamartomatous polyp, interstitial edema, eosinophil infiltration, cystic dilation of glands*

INTRODUCTION

Cronkhite–Canada syndrome (CCS) refers to a group of clinical syndromes first reported by Cronkhite and Canada in 1955,[1] mainly characterized by gastrointestinal polyps and the presence of the ectodermal triad syndrome (alopecia, cutaneous hyperpigmentation, and onychodystrophy). It is a rare disease with an incidence rate of 1 per million; its etiology remains unknown. The disease is thought to be linked to infections, autoimmunity, vitamin deficiency, mental stress, and fatigue, but the primary causes are probably immunity-related. Although there are no specific algorithms or standards for CCS diagnosis, the endoscopic and pathological assessment of gastrointestinal polyps plays a crucial role in the process. This study analyzes and summarizes various clinical characteristics of CCS, aiming to facilitate an early diagnosis in affected individuals.

MATERIALS AND METHODS

Case Selection

The study is a retrospective analysis of cases reported between January 2010 and January 2020, available in major databases, for example, the Chinese Biomedical Literature Database (CBM Web), the China Academic Journals Full-text Database (CJFD), and PubMed. Only cases that met the following 2 criteria were included: (1) having a clear endoscopic description and endoscopic imaging documentation and (2) having a pathological assessment of the endoscopic biopsy or the resected polyps. We retrieved 97 case reports or case series on CCS on PubMed, after excluding the absence of pictures and related descriptive case reports, 50 articles remained, containing 52 CCS cases. In addition, CBM Web and CJFD Chinese databases were searched, and 63 articles related to CCS were retrieved. Using the same exclusion criteria,

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23 articles were included, with a total of 24 patients with CCS. Therefore, an overall total of 76 patients was included based on the Chinese and PubMed databases. We chose to include cases after 2010 because earlier studies often lacked endoscopic and pathological pictures or included poor-quality images, which would have affected our results and eventually disturbed the accuracy of our statistical analysis.

Observation Indicators

The study collected endoscopic descriptions and images as well as pathological assessments of the reported cases. We adopted a retrospective analysis method, summarized case data with Microsoft Excel software, and statistically analyzed endoscopic observation indicators and pathological results. The main focus points of endoscopic assessments included the overall distribution and main distribution sites of polyps; the distribution characteristics of polyps (Figs. 1-5) such as (1) carpet-like or clustered (dozens of polyps merging into a plate or a cluster), (2) densely distributed (featuring large numbers and high density where less than 10 polyps merge together), (3) with a high frequency of occurrence (large numbers yet low merging), and (4) scattered (small numbers with scattered distribution); polyp color; polyp sizes ≤10, 10-20, and ≥20 mm; and polyp shape, which was either pedunculated or sessile. The enteroscopy and capsule endoscopy allowed for the observation of characteristics of polyps and small intestinal villi. The main pathological observations related to polyps included: the pathological types of upper gastrointestinal endoscopic and colonoscopic polyp biopsies, interstitial edema of polyps, eosinophil infiltration, and cystic dilatation of glands. The aim of this study was to better define the characteristics of the disease by analyzing the incidence of endoscopic and pathological features in CCS patients, so as to provide a basis for earlier diagnoses.

Main Points

- *Cronkhite–Canada Syndrome (CCS)**:** CCS is a rare non-familial polyposis syndrome characterized by multiple gastrointestinal polyps with an ectodermal triad. Although there is no specific algorithm or standard for the diagnosis of CCS, endoscopic and pathological assessment of digestive tract polyps plays a crucial role in this process. At present, systematic analysis of endoscopic and pathological characteristics of CCS polyps is rare.*
- *Endoscopic characteristic of CCS**:** CCS polyps are distributed in the whole gastrointestinal tract, especially in the stomach. Polyps are densely distributed and tend to merge. They may appear in carpet or cluster distribution, most of which are bright red. The majority of gastric polyps are flat and non-pedunculated, whereas colorectal polyps are a mixture of sessile and pedunculated polyps. Small intestine polyps are also common in the CCS cases in which small intestine villi become swollen, longer, and sometimes resemble waterweeds.*
- *Pathological features of CCS**:** The pathological assessment of CCS polyps shows that both gastric polyps and intestinal polyps are mainly juvenile hamartomatous polyps and have a high malignant transformation rate of more than 15%. Interstitial edema, eosinophil infiltration, and cystic dilation of glands are common features of CCS polyps, and their presence distinguishes CCS from other gastrointestinal polyposis syndromes.*
- *Differentiation of CCS from other polyp syndromes**:** CCS is characterized by the presence of multiple polyps in the gastrointestinal tract and constitutes a different disease entity than familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, juvenile polyposis syndrome (JPS), Cowden syndrome, and other diseases. CCS polyps have a tendency of fusion and can be distributed in a carpet or cluster shape. The polyps and the mucosa between polyps are also hyperemic and edema. These characteristics are unique to CCS polyps and can be distinguished from other polyps. Interstitial edema, eosinophil infiltration, and cystic dilation of glands are common features of CCS polyps, and their presence distinguishes CCS from other gastrointestinal polyposis syndromes.*

Statistical Analysis

Statistical Package for the Social Sciences 19.0 software was used for statistical analysis. Measurement data were tested for normality. Normally distributed data were expressed as mean ± standard deviation. Non-normally distributed data were expressed as median (interquartile range), and nonparametric tests were used for comparative analyses.

RESULTS

Basic Information

Among the 76 cases, 24 cases were retrieved from the Chinese databases and 52 cases were from the Pubmed database. Seventy-five cases had detailed descriptions of upper gastrointestinal endoscopy; 74 cases had detailed descriptions of colonoscopy; only 4 cases included enteroscopic data and 6 cases capsule endoscopic data; 63 cases had complete pathological data, while the remaining 13 cases only included incomplete pathological data (Table 1).

Table 1. Endoscopic and Pathological Statistics of the Patients

Number	Author	PD	Upper Gastrointestinal Endoscopy				Colonoscopy				Enteroscopy		CE		Pathology		
			DC	Color (BR)	Sizes	Shape	DC	Color (BR)	Sizes	Shape			Gastrodudenal	Colorectum	IE	EI	CDG
1	Bin	2016	1	Y	1	1	2	Y	1	1			3	1+2	Y	Y	N
2	Chen	2014	2	Y	1	1	3	Y	1	1			1	1+2	Y	Y	N
3	Wang	2019	3	N	1	1	2	N	1	1			1	1	Y	N	N
4	Wang	2019	3	N	1	1	2	N	1	1			1	1	Y	N	N
5	Chen	2013	1	Y	2	1+2	3	Y	3	1+2			3	3			
6	Liu	2014	1	Y	2	1	3	Y	3	1+2			3	3	Y	N	Y
7	Chao	2017	1	Y	2	1	2	Y	3	1+2			1	2	Y	N	N
8	Gao	2018	2	Y	1	1	1	Y	1	1			3	3	Y	N	Y
9	Ni	2014	1	Y	2	1	4	Y	3	1+2			1	2			
10	Hua	2010	1	Y	1	1	3	Y	1	1+2			3	3	Y		Y
11	Jiang	2018	3	Y	1	1	2	Y	1	1			1	2	Y	Y	N
12	Lian	2013	1	Y	2	1	2	Y	2	1+2			1	2	Y	Y	N
13	Liu	2013	2	Y	2	1+2	2	N	2	1+2			3+1	1	Y	Y	N
14	Wang	2017	2	Y	1	1	2	Y	1	1			1	1	Y	Y	N
15	Zhang	2015	1	Y	2	1+2	2	Y	3	1+2			3	3	Y	Y	Y
16	Li	2011	1	Y	3	1+2	2	Y	2	1+2	Scattered		1	1+2	Y	N	N
17	Yang	2017	2	Y	1	1	3	Y	1	1			3	3	Y	N	Y
18	Gong	2010	2	Y	3	1	3	Y	2	1				1	Y	Y	Y
19	Yuan	2015	1	Y	1	1	2	Y	2	1+2			3	1			
20	Tang	2013	1	Y	2	1	1	Y	2	1+2			1+3	1+2	Y	Y	Y
21	Hu	2018	2	Y	2	1	1	Y	2	1+2			3	3	Y	N	Y
22	Cheng	2011	3	Y	1	1	2	Y	1	1		WE	3	1	Y	N	Y
23	Xi	2014	2	Y	1	1	1	Y	2	1+2			1	1+2	Y	N	N
24	Wang	2020	1	Y	2		1	Y	3	1+2	Scattered	WE/ WLM	3	2	Y	Y	N
25	Faria	2018	2	Y	2	1+2	1	Y	2	1+2							
26	Seshadri	2012	1	Y	2	1	3	Y	2	1+2			3	3+2,Ca	Y	Y	Y
27	Watari	2011	1	Y	1	1	1	Y	3	1+2				2,Ca	Y	N	Y
28	Sweetser	2010	3	Y	1	1	2	Y	3	1+2			3	3+2	Y	N	Y

(*Continued*)

Table 1. Endoscopic and Pathological Statistics of the Patients (*Continued*)

Number	Author	PD	Upper Gastrointestinal Endoscopy				Colonoscopy				Enteroscopy		CE		Pathology		
			DC	Color (BR)	Sizes	Shape	DC	Color (BR)	Sizes	Shape			Gastrodudenal	Colorectum	IE	EI	CDG
29	Urabe	2015	1	Y	1	1	1	Y	1	1				3	Y	N	Y
30	Matsui	2011	2	Y	2	1+2	3	Y	2	1+2				Ca			
31	Tanaka	2019	1	Y	2	1+2	2	Y	1	1			3	3	Y	N	Y
32	Zhu	2015	2	Y	1	1	2	Y	2	1+2			3	2+3,Ca	Y	N	Y
33	She	2013	1	Y	1	1	3	Y	2	1+2		WE					
34	Mao	2019	3	Y	2	1	3	Y	2	1+2			3	2	Y	N	Y
35	Murata	2017	1	Y	2	1	2	Y	1	1	Scattered		3	3	Y	Y	Y
36	Qun	2015	2	Y	2	1	3	Y	2	1+2			1	1	Y	Y	N
37	Dawra	2017	1	Y	1	1							3	3	Y	Y	Y
38	Christopher	2014	2	Y	2	1+2	3	Y	3	1+2			3	3			
39	Nemade	2017	1	Y	2	1	3	Y	1	1			3	2+3			
40	Brigid	2016	3	Y	1	1	2	Y	2	1+2			3	3+2	Y	N	Y
41	Subrata	2015	2	Y	1	1	2	Y	1	1			3	3	Y	Y	Y
42	Wang	2016	2	Y	1	1	1	Y	2	1+2			3	1+2,Ca	Y	Y	Y
43	Suzuki	2009	1	Y	1	1	2	Y	1	1					Y	N	Y
44	Yuan	2010	1	Y	3	1	1	Y	2	1+2		WE/ WLM					
45	Yun	2013	2	Y	1	1	2	Y	2	1+2		WE/ WLM	3	2+5,Ca	Y	N	Y
46	Maruno	2011	2	Y	2	1	1	Y	3	1+2			3	2,Ca	Y	N	Y
47	Yamanouchi	2016	1	Y	1	1	2	Y	1	1			Ca	Ca			
48	Isobe	2013	1	Y	2	1+2	3	Y	3	1+2			1,Ca	1+2,Ca	Y	Y	Y
49	Fan	2016	2	Y	3	1	2	Y	3	1+2			3	3+5	Y	Y	Y
50	Seisuke	2015	1	Y	1	1	1	Y	1	1					Y	N	Y
51	John	2012	1	Y	2	1+2	2	Y	2	1+2							
52	Woohee	2018	1	Y	1	1	2	Y	2	1			1	3	Y	N	Y
53	Fuyuno	2017	1	Y	2	1	3	Y	3	1+2			Ca				
54	Nitin	2017	2	Y	1	1	3	Y	2	1			1	1			
55	Xue	2013	2	Y	1	1	2	Y	2	1				1+2			
56	Yuan	2017	2	Y	3	1+2	3	Y	3	1+2			1	2	Y	N	N

(*Continued*)

Table 1. Endoscopic and Pathological Statistics of the Patients (*Continued*)

Number	Author	PD	Upper Gastrointestinal Endoscopy				Colonoscopy				Enteroscopy	CE		Pathology		
			DC	Color (BR)	Sizes	Shape	DC	Color (BR)	Sizes	Shape		Gastrodudenal	Colorectum	IE	EI	CDG
57	Zhao	2016	1	Y	2	1	3	Y	2	1+2		1	4			
58	Dhrubajyoti	2016	2	Y	2	1	3	N	1	1	Scattered	3	2	Y	N	Y
59	Patil	2012	3	Y	2	1	4	Y	1	1		3	3	Y	N	N
60	Patil	2012	3	Y	2	1	4	Y	1	1						
61	Taylor	2018	2	Y	2	1								Y	Y	Y
62	Aoun	2011	1	Y	2	1	4	Y	3	1+2		3	3	Y	N	Y
63	Traussnigg	2016	1	Y	3	1+2	2	Y	3	1+2		1	1	Y	Y	Y
64	Yamakawa1	2016	1	Y	1	1	3	Y	1	1		3	3	Y	N	Y
65	Yamakawa1	2016	3	Y	2	1	2	Y	2	1+2		3	3	Y	Y	Y
66	Watari	2011	1	Y	1	1	2	Y	2	1+2		3,Ca	2,Ca	Y	N	Y
67	Sharma	2018	1	Y	3	1+2	3	Y	2	1+2		3	3			
68	Douglas	2019					1	Y	2	1+2		3	3	Y	N	N
69	Ashish	2016	2	Y	1	1	3	Y	2	1+2		3	3	Y	Y	Y
70	Rani	2016	2	Y	1	1	1	Y	2	1+2		3	3	Y	Y	N
71	Morino	2018	1	Y	3	1+2	3	Y	1	1+2			3	Y	N	Y
72	Langevin	2018	1	Y	3	1+2	2	Y	2	1+2						
73	Timothée	2016	1	Y	1	1	2	Y	2	1	WLM			Y	N	Y
74	Kato	2013	2	Y	1	1	4	Y	2	1			Ca	Y	Y	Y
75	Y.L.Lo	2016	3	Y	1	1	3	N	2	1+2		1	2+3	Y	Y	Y
76	Ueyama	2012	3	Y	2	1	3	Y	3	1+2		3	2	Y	N	Y

Distribution characteristics:1, carpet-like or clustered;2, densely distributed;3, Multiple distributed;4, scattered. Sizes: 1, ≤ 10 mm; 2, 10–20 mm; 3, ≥ 20 mm. Shipe: 1, Yamada Type I & Type II; 2, Yamada Type III & Type IV. Pathological type: 1, hyperplastic; 2, adenomatous; 3, hamartomatous (including juvenile); 4, inflammatory; 5, serrated adenoma.
DC, Distribution characteristics; BR, bright red; GE, upper gastrointestinal endoscopy; PD, published data; CE, capsule endoscopy; IE, interstitial edema; EI, eosinophil infiltration; CDG, cystic dilatation of glands; WLM, waterweed-like morphology; WE, villi edema; Ca, cancer; GI, gastrointestinal; Y, yes; N, none.

Gastroscopic Data of CCS

Distribution Locations

In the 75 cases with upper gastrointestinal endoscopy, no esophageal polyps were found; gastric polyps were found in all the cases; duodenal polyps were found in 42 cases (56%). Regarding the main location of gastric polyps, there were 15 cases of whole-stomach diffuse polyposis (20%), 2 cases of polyps mainly distributed in the duodenum (2.67%), and 58 cases of polyps in the gastric antrum (77.33%), among which 31 cases only had gastric antrum as the sole location. In comparison, 26 cases had both gastric antrum and gastric body as polyp locations.

Distribution Characteristics

There were 37 cases (49.33%) with carpet-like or clustered polyps, 26 cases (34.67%) with dense distribution, 12 cases (16.00%) with a high frequency of occurrence, and none with the scattered distribution. There were 63 cases of polyp fusion (37 + 26, 84.00%).

Polyp Color

There were 73 cases (97.33%) of bright red and 2 cases (2.67%) of non-bright red colors.

Sizes and Shapes of Polyps

The cases were divided into 3 groups according to the polyp sizes: ≤10, 10-20, and ≥20 mm, and into 2 groups according to their shapes: pedunculated (Yamada Type III & Type IV) and sessile (Yamada Type I & Type II). There were 35 cases (46.67%) with a polyp size less than or equal to 10 mm, all of them were sessile; 31 cases (41.33%) with a size between 10 and 20 mm, among which 9 cases had both pedunculated and sessile polyps, and 22 cases only had sessile polyps; 9 cases (12.00%) were characterized by polyp size greater than or equal to 20 mm, and had both pedunculated and sessile polyps.

Colonoscopy Data of CCS

Distribution Locations

Polyps were found in all of the 74 colonoscopical cases, among which 22 cases (29.73%) also had terminal ileal polyps. Regarding the locations of intestinal polyps, 6 cases (8.11%) were mainly localized in the terminal ileum and ileocecal junction, whereas all the other cases had polyps distributed in the whole colon.

Distribution Characteristics

There were 14 cases (18.92%) with carpet-like or clustered polyps, 30 cases (40.54%) with dense distribution, 25 cases (33.78%) with high-frequency occurrence, and 5 cases (6.76%) with the scattered distribution. There were 44 cases of fused polyps (14 + 30, 58.46%).

Polyp Colors

There were 69 cases (93.24%) of bright red and 5 cases (6.76%) of non-bright red colors.

Sizes and Shapes of Polyps

There were 23 cases (31.08%) with polyps smaller or equal to 10 mm, among which 21 cases were sessile, and 2 cases had mixed pedunculated and sessile polyps; 34 cases (45.95%) had a size between 10 and 20 mm, among which 28 cases (82.35%) had both pedunculated and sessile polyps, and the remaining 6 cases (17.65%) only had sessile polyps; 17 cases (22.97%) had polyps with a size ≥20 mm, which were all mixed pedunculated and sessile polyps. Among the 51 cases with the polyp size ≥10 mm, the polyps showed mainly mixed pedunculated and sessile morphology, accounting for 45 cases (88.24%).

Enteroscopic and Capsule Endoscopic Data of CCS

Among the 75 cases, only 4 cases underwent enteroscopy and 6 cases underwent capsule endoscopy. In all the cases, polyps were found scattered throughout the small intestine. The capsule endoscopy had some magnifying effect on the mucosa, allowing for the detection of swollen and longer villi, while some of them were characterized by waterweed-like morphology (Fig. 6).

Pathological Assessment

Pathological Type

Sixty-six cases included upper gastrointestinal endoscopy- and colonoscopy-based pathological assessments, among which 4 reports only characterized cancerous tissue without describing the polyps. There were 62 cases with pathological assessment of colorectal polyps, and 57 cases with pathological assessment of gastroduodenal polyps. The polyp pathology included the following types: hyperplastic, adenomatous, hamartomatous (including juvenile), inflammatory, and serrated adenoma. The pathological type of the upper gastrointestinal endoscopy cases was dominated by hamartomatous polyps with 37 cases (64.91%), followed by hyperplastic polyps with 18 cases (31.58%). There were 2 cases with mixed-type polyps (3.51%), which contained both hyperplastic and hamartomatous polyps. Malignant transformation was detected in 4 out of 57 patients, accounting for 7.02% of

cases. Among the pathological types of colorectal polyps, there were 22 cases (35.48%) of hamartomatous polyps, 12 cases (19.35%) of adenomatous polyps, 10 cases (16.13%) of hyperplastic polyps, 1 case (1.61%) of inflammatory polyps, and 17 cases (27.42%) of mixed-type polyps. Malignant transformation was detected in 11 out of 62 patients, accounting for 17.74% of cases.

Pathological Characteristics

The study focused on 3 aspects, namely interstitial edema, eosinophil infiltration, and cystic dilation of glands. Fifty-eight reports included pathological assessments, and all of them described interstitial edema; 25 cases (43.10%) contained descriptions of eosinophil infiltration; and 41 cases (70.69%) contained descriptions of cystic dilation of glands.

Differentiation from Other Gastrointestinal Polyps

CCS is characterized by the presence of multiple polyps in the gastrointestinal tract and constitutes a different disease entity than familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, juvenile polyposis syndrome (JPS), Cowden syndrome, and other diseases. Endoscopic assessments mainly identified the locations and distribution characteristics of polyps, their numbers, colors, sizes, and shapes. Pathological assessments mainly identified pathological types of polyps, rates of malignant transformation, interstitial edema, eosinophil infiltration, and cystic dilation of glands (Tables 2). Similar to several other gastrointestinal polyps, as shown in Table 2, CCS is characterized by the distribution of polyps throughout the gastrointestinal tract. This is most similar to the polyp distribution in Cowden disease, in which polyps are typically found in the stomach and colon. By comparison, the polyps of Peutz-Jeghers syndrome are mainly distributed in the small intestine, while those in familial adenomatous polyposis and juvenile polyposis mostly occur in the colorectal regions. From the perspective of distribution characteristics, CCS and familial adenomatous polyposis tend to have more polyps, which can lead to dense and multiple growths. However, while CCS polyps are prone to fusion, those in familial adenomatous are not. Peutz-Jeghers syndrome, juvenile polyposis, and Cowden disease tend to have slightly fewer polyps, most of which are multiple or scattered in distribution. The morphology of polyps is often correlated with their size. Pedicled polyps over 3.0 cm can occur in familial adenomatous polyposis, Peutz-Jeghers syndrome, and juvenile polyposis. CCS and Cowden disease are mostly characterized by flat polyps smaller than 2 cm, but those in CCS can merge

Table 2. Endoscopic and Pathological Characteristics and Differentiation of Gastrointestinal Polyposis

	Distribution Characteristics	Diagnostic Characters	No. of Polyps	Polyp Colors	Polyp Sizes	Polyp Shapes	Pathological Type of Gastric Polyps	Pathological Type of Colorectal Polyps	Lifetime Risk of Cancer	Interstitial Edema	Eosinophil Infiltration	Cystic Dilatation of the Glands
Cronkhite–Canada syndrome (CCS)	Entire gastrointestinal (GI) tract. Stomach>colorectum>small intestine	Polyp fusion, carpet-like or clustered	Hundreds to thousands (the greatest number)	Hyperemia of polyps and peripheral mucosa	Most polyps are Smaller than 20 mm	Sessile polyps are dominant	Hamartomatous	Hamartomatous, Adenomatous	15%	Almost all	High incidence	High incidence
Familial adenomatous polyposis (FAP)	Entire GI tract. Colorectum>stomach, small intestine	Colonic dense distribution	Hundreds to thousands	Hyperemia in some polyps	Polyps of different sizes, larger than 20 mm is common	Pedicle polyps are common	Fundic gland polyps, adenomatous	Adenomatous	100%	Rare	Rare	Rare
Peutz-Jeghers syndrome	Entire GI tract. Small intestine>colorectum>stomach	Mainly distributed in the small intestine	Often more than 100	Hyperemia in some polyps	The size varies from 60 to 80mm.	A mixture of pedunculated and not pedunculated	Hamartomatous	Hamartomatous, Adenomatous	40-80%	Rare	Rare	Common
Juvenile polyposis syndrome (JPS)	Entire GI tract. Colorectum common,stomach and small intestine rare	Mainly colorectal distribution	Few, rarelyds 100	Hyperemia is More common	They vary in size from 5 to 50 mm	Pedunculated polyps are common	Juvenile	Juvenile	20-40%	Common	Rare	Common
Cowden syndrome	Entire GI tract. Stomach>colorectum>small intestine, esophagus	Esophageal polyps withglycogen acanthosis are more common	More than 100	Hyperemia of The polyps is rare	Most polyps are smaller than 20 mm	Sessile polyps are dominant	Hamartomatous	Hamartomatous	10%	Rare	Rare	Rare

into clustered growths. In terms of the pathological types of polyps, patients with CCS, Peutz-Jeghers syndrome, juvenile polyposis, and Cowden disease typically contain hamartomatous polyps, the pathological characteristics of which are similar among CCS and juvenile polyposis. Familial adenomatous polyposis is dominated by adenomatous polyps. These 5 types of gastrointestinal polyposis having high cancerization rate, with the cumulative rate exceeding 10%, and reaching up to 100% in familial adenomatous polyposis. Interstitial edema and eosinophil infiltration are more common in patients with CCS than in several other types of gastrointestinal polyposis. The cystic dilatation of polyp glands is characteristic of hamartoma polyps and is, therefore, more common in CCS and Peutz-Jeghers syndrome, juvenile polyposis, and Cowden disease, but less common in familial adenomatous polyposis.

DISCUSSION

CCS is a non-hereditary disease, which is different from several other common gastrointestinal polyposis syndromes. Common clinical manifestations of this disease include chronic diarrhea, anorexia, hypogeusia, emaciation, and cutaneous hyperpigmentation, among others,[2] most of which are generally typical to gastrointestinal diseases. Upper gastrointestinal endoscopy and colonoscopy are important and common diagnostic techniques. Therefore, understanding the endoscopic and pathological characteristics of CCS is of great significance for the proper and timely diagnosis of the condition.

The presence of multiple polyps in the gastrointestinal tract is an important feature of CCS. In the 76 cases assessed in this study, both gastric and colon polyps were always found, while no esophageal polyps were detected. Statistical analysis by Luo et al.[3] and Watanabe et al.[4] showed that esophageal polyps had been found in a small number of CCS patients indeed. Those 2 retrospective studies found that the incidence of esophageal polyps in CCS was 11.5% (3/26) and 12.4% (26/210), respectively. Most of the esophageal biopsies revealed nonspecific inflammation, and some showed squamous papilloma of the esophagus. All the enteroscopic and capsule endoscopic assessments revealed the presence of small intestinal polyps. Therefore, polyps of CCS are distributed throughout the gastrointestinal tract, with gastric polyps being the most common. This feature differs CCS from FAP, Peutz-Jeghers syndrome, and JPS, but is also found in patients with Cowden syndrome. Gastric polyps of CSS are characterized by denser distribution in the gastric antrum, higher fusion rate, and carpet-like or clustered distribution.[5] Polyps of CSS are likely to fuse, and it is common that multiple or even dozens of polyps are connected to each other without obvious boundaries, forming carpet-like or clustered structures.[6] Such distribution is seen in 84% of gastric polyps and 58.46% of colon polyps, while it is rare in other gastrointestinal polyposis syndromes. Hence, fusion and carpet-like distribution can be seen as a hallmark of CCS polyps.

In this study, 97.33% of CCS gastric polyps and 93.24% of intestinal polyps were bright red. The mucous membrane around the polyps was also characterized by hyperemia and edema. The more densely distributed and the brighter the polyps were, the more significant the hyperemia and edema was in the mucous membrane around the polyps, and the more severe the clinical symptoms appeared. Therefore, the color of polyps may be to some extent related to their number and to the severity of the disease. In all the cases, the pathology of CCS polyps suggested interstitial edema, which could explain why the polyps were bright red. Bright red polyps can also be found in other gastrointestinal polyposis syndromes, but the colors are often related to the size of polyps. In those other conditions, bigger polyps are usually characterized by a richer blood supply, which results in brighter colors.

The majority (88%) of gastric polyps in the CCS cases are smaller than 20 mm, and their morphology is mainly sessile. Specifically, polyps smaller than 10 mm are all sessile, while 82.35% of the polyps between 10 and 20 mm are sessile. Polyps larger than 20 mm are rare and are characterized by mixed pedunculated or sessile morphology. Likewise, the size and shape of colorectal polyps are also related to a certain extent.[7] Polyps smaller than 10 mm are mainly sessile, while those over 20 mm are mainly pedunculated. There is no significant difference between the characteristics of CCS colorectal polyps and those found in other gastrointestinal polyposis syndromes. Gastric polyps are small and flat with a salmon-like shape,[6] and can be easily distinguished from those of other conditions.

Polyps were found in the small intestine in all examined cases and were mainly sessile. Capsule endoscopy revealed that the villi in the entire small intestine were characterized by hyperemia and became longer, while some of the cases showed waterweed-like changes, which is uncommon in other diseases. Such changes are consistent with the presence of interstitial edema as

suggested by pathological data, but we cannot conclude yet whether they are a hallmark of CCS (due to the limited number of reports.[8,9] Moreover, the enteroscopy and capsule endoscopy data revealed the presence of atrophic villi, manifested as flat surfaces on the intestinal mucosa. The 2 different conditions can be manifestations of CCS at different stages.[10]

CCS is considered to be a hamartomatous polyposis syndrome, the pathology of which is extremely similar to that of the JPS; however, those 2 conditions are accompanied by other types of polyps.[11-14] This is consistent with the data of our analysis, as we found that 64.91% of gastric polyps were hamartomatous polyps, while the remaining polyps were hyperplastic. Colorectal polyps are mainly hamartomatous and adenomatous, but hyperplastic polyps could be seen in quite a few cases as well. Polyps in CCS patients also have a higher rate of malignant transformation, and our data show a rate of 7.02% of malignant transformation among the cases with gastric polyps and 17.84% among those with colorectal polyps, which is consistent with the data reported by Watanabe et al.[4] According to Yashiro et al.,[15] apart from the classic cancerous growth from adenomatous polyps, there is also a possibility of malignant transformation in serrated adenoma.[16] The process of canceration of gastric polyps is different from that of colon polyps as chronic mucosal inflammation may increase the risk of malignant transformation, analogically to mutation-inducing inflammation occurring in the idiopathic inflammatory bowel disease.[17,18] Interstitial edema was detected in all the CCS cases assessed pathologically, indicating that it is a typical polyp feature in this condition. Of note, interstitial edema is rarely seen in other gastrointestinal polyposis syndromes except for the JPS; moreover, interstitial edema is also common in the mucosa between polyps in the CCS cases—a feature not found in any other polyposis types, and thus highly important for the CCS diagnosis.[19-20] Our data indicate that eosinophil infiltration is very common in polyps of the CCS cases, accounting for a rate as high as 43.10%. On the other hand, eosinophilia is uncommon in other gastrointestinal polyposis syndromes, indicating that eosinophil infiltration is a characteristic feature that may be used during CCS diagnosis. In addition, cystic dilation of glands occurs in 75.85% of CSS cases, which is consistent with the characteristics of hamartomatous polyps.

CCS is also a type of gastrointestinal polyposis, which needs to be distinguished from familial adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis, Cowden disease and other types of gastrointestinal polyposis. CCS polyps are distributed along the entire digestive tract and are more frequent and denser in the stomach than polyp fusion. Cowden disease also has a dominant distribution of polyps in the stomach, but polyps in patients with CCS are more frequent and undergo fusion, making them unique compared to other polyps. Pathological types of CCS are very similar to juvenile polyps, except that the mucosa between CCS polyps also has inflammatory changes, almost all polyps have interstitial edema, and nearly half have eosinophil infiltration. According to their endoscopic and pathological characteristics, CCS polyps can be distributed on the mucosal surface like carpets or clusters. There was also interstitial edema and eosinophil infiltration, and inflammatory edema was also found in the mucosa between the polyps. These characteristics are often not found in other forms of gastrointestinal polyposis and may therefore be helpful in distinguishing the different types.

At present, the largest studies conducted with different populations are the national CCS patient survey by Watanabe et al. from Japan (210 cases) and the retrospective study by Chao et al. from China on all CCS patients reported in China (83 cases). The conclusions of these studies are largely consistent with this study. Patients with CCS display gastrointestinal polyposis involving complete digestion, especially in gastric lesions, and their polyps are denser. The histological examination of polyps mainly focused on hamartoma, with cystic dilatation, eosinophilic granulocyte infiltration, and hyperemia and edema of polyps and interpolyp mucosa. In contrast to these previous studies, we found that CCS gastric polyps are mainly distributed in the gastric antrum and body and that they can be fused into pieces to form carpet-like distribution. Colonic polyps are prominent in the ileocecal region and may fuse to form a carpet- or cluster-like distribution. The characteristics of the small intestine were also summarized, and it was found that CCS could involve the mucosa of the whole small intestine and that hyperemia, prolongation, aquatic changes and villi atrophy could occur in the villi. Polyp pathology revealed that interstitial edema occurred in all patients with CCS, and eosinophil infiltration was also characteristic of other gastrointestinal polyps.

This study has some limitations. First of all, the number of cases of small intestinal examination was relatively small, and descriptions of more cases will be needed in order to representatively report the characteristics of small intestinal polyps and changes in mucosal villi. Second,

the etiology of CCS is mainly considered to be related to autoimmunity, especially to IG-4-related inflammation. However, only a few from the collected cases in this study involved etiological assessments. Therefore, this paper failed to explore the etiology and pathogenesis of CCS. Finally, because of the content of the study, we excluded some cases whose endoscopic images were incomplete or pathological descriptions were not detailed, so the results of the study may be one-sided, and more detailed cases are needed to support the discussed data.

In conclusion, CCS is a gastrointestinal polyposis mainly featuring bright red, gastric polyps, which are characterized by dense distribution and a tendency to fuse. The more polyps and the denser their distribution, the brighter their color.[21,22] Small intestine polyps are also common in the CCS cases in which small intestine villi become swollen, longer, and sometimes resemble waterweeds. The pathological assessment of CCS polyps shows that both gastric polyps and intestinal polyps are mainly juvenile hamartomatous polyps and have a high malignant transformation rate of more than 15%. Interstitial edema, eosinophil infiltration, and cystic dilation of glands are common features of CCS polyps, and their presence distinguishes CCS from other gastrointestinal polyposis syndromes. In line, studying the endoscopic and pathological characteristics of CCS can greatly contribute to early diagnosis and timely treatment of the disease.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Binzhou Medical University Hospital.

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study and clinical and pathologic data of the patients were de-identified and analyzed anonymously.

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