Case Report

Cronkhite-Canada Syndrome: The First Case Series in Thai Population

Mati Chuamanochan MD[1], Napatra Tovanabutra MD[1], Pongsak Mahanupab MD[2], Sarawut Kongkarnka MD[2], Siri Chiewchanvit MD[1]

[1] Division of Dermatology, Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand
[2] Department of Pathology, Chiang Mai University, Chiang Mai, Thailand

The authors reported three Thai patients diagnosed with Cronkhite-Canada Syndrome [CCS]. All patients presented with chronic diarrhea resulting from gastrointestinal [GI] polyposis and the characteristic cutaneous findings, hyperpigmented skin, nail dystrophy, and/or hair loss. CCS is uncommon worldwide, with only one previously reported case from Thailand. To the authors knowledge, this was the first case series of Thai CCS patients. In the present report, the authors summarized the epidemiologic and clinical information of the Thai patients and compared them to the data from other countries. The frequency of each cutaneous finding and the histologic type of the polyps differed between Thai patients and other ethnic groups.

Keywords: Cronkhite-Canada syndrome, First case series, Thai population

J Med Assoc Thai 2018; 101 (11): 1599-604
Website: http://www.jmatonline.com

Cronkhite-Canada Syndrome [CCS] presents with gastrointestinal [GI] polyposis and a triad of cutaneous abnormalities including nail dystrophy, alopecia, and hyperpigmentation of the skin[1]. These cutaneous findings are very important to the diagnosis of CCS. The etiology is not well elucidated. The mainstay of treatment is systemic corticosteroids. Most of the cases are Europeans and Japanese[2]. A review of literature showed only one previous case report of a Thai CCS patient, in 1981[3]. Therefore, the authors is reporting the first case series of three CCS patients in the Thai population.

Materials and Methods

The authors retrospectively reviewed the medical records of the patients at the Dermatology Clinic, Division of Dermatology, Department of Internal Medicine, Chiang Mai University, Thailand, between January 1990 and January 2016. The clinical information, including sex, age, presenting symptoms, comorbidities, cutaneous manifestations, GI involvement, and treatment were collected. For the histopathology of GI polyps, the tissues were also stained using IgG (Dako, Glostrup, Denmark) and IgG4 (Ventana, California, USA) antibodies with a streptavidin-biotin detection system. The degree of immunohistochemistry staining of the inflammatory cells per high power field [HPF] was classified as few (0 to 4/HPF), slight (5 to 10/HPF), moderate (10 to 30/HPF), and severe (more than 30/HPF), as proposed by Kamisawa et al[4].

Correspondence to:

Chiewchanvit S. Division of Dermatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, 110 Intawarorot Raod, Sriphum District, Chiang Mai 50200, Thailand.
Phone: +66-53-935482, **Fax**: +66-53-935481
Email: drsiri2010@gmail.com

Results

Three patients were diagnosed with CCS. All patients presented with chronic diarrhea. One patient also complained of hypogeusia as a co-presenting symptom. Endoscopic studies of all three patients revealed polyposis along the GI tract with sparing of the esophagus. The histopathologic studies of the polyp biopsies in all patients demonstrated similar findings, composed of many cystically dilated and tortuous crypts containing inspissated mucin among edematous lamina propria with increased numbers of lymphocytes, plasma cells and eosinophils (Figure 1, 2). Neither dysplasia nor invasive malignancy was observed. The diagnosis was hamartomatous polyposis consistent with CCS-associated polyps. IgG4 immunohistochemistry staining of a colonic polyp was performed in case 1 and demonstrated slight IgG4 plasma cell infiltration, approximately 5/HPF (Figure 3).

For dermatologic examination, one patient (case 1) had the complete triad of cutaneous abnormalities, while the other two patients had onychodystrophy and

How to cite this article: Chuamanochan M,Tovanabutra N, Mahanupab P, Kongkarnka S, Chiewchanvit S. Cronkhite-Canada syndrome: the first case series in Thai population. J Med Assoc Thai 2018;101:1599-604.

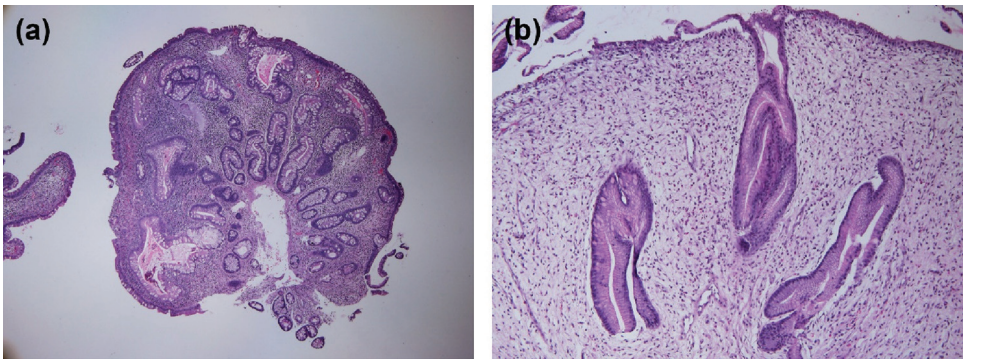

Figure 1. (a) Low power view of an ileal polyp showing many elongated and irregular crypts associated with inflammation in the lamina propria. (b) Intermediate power view of a gastric polyp showing elongated and tortuous foveolar epithelium as well as lamina propria expansion (Hematoxylin and eosin, 4x and 10x).

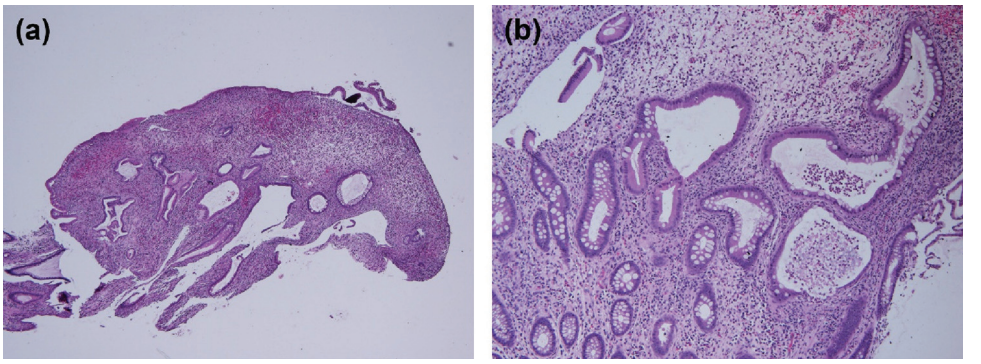

Figure 2. (a) Low power view of a colonic polyp showing irregular and cystically dilated crypts associated with an edematous lamina propria containing mononuclear inflammatory cells and eosinophils. (b) Intermediate power view of a colonic polyp closely resembling juvenile polyp (Hematoxylin and eosin, 4x and 10x).

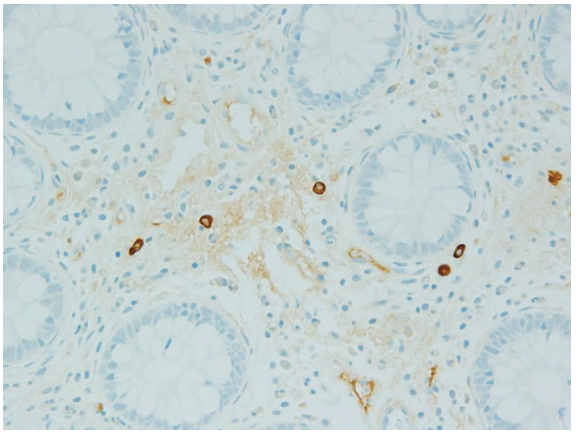

Figure 3. IgG4 immunohistochemistry of a colonic polyp revealing slight IgG4 plasma cell infiltration (40x).

hyperpigmentation of palms and soles but no evidence of alopecia. The cutaneous findings in all cases and the comparative dermatologic findings before and six months after treatment in case 1 are presented in Figure 4-6.

The clinical information of the three patients in the present study and the one previously reported Thai case is summarized in Table 1.

Discussion

In the present review, we summarized and compared the epidemiologic and clinical information from the five case-series from different countries including the four cases from Thailand (three cases in the present case series and one previously reported case). The authors have found that most Thai patients were in their fifties, similar to the other case series, but male was slightly more common than in other ethnic series. Diarrhea was the most common symptom in the Thai patients. Regarding dermatologic findings, all Thai patients had onychodystrophy and hyperpigmentation, but only one half of them had alopecia. These findings differed from the other

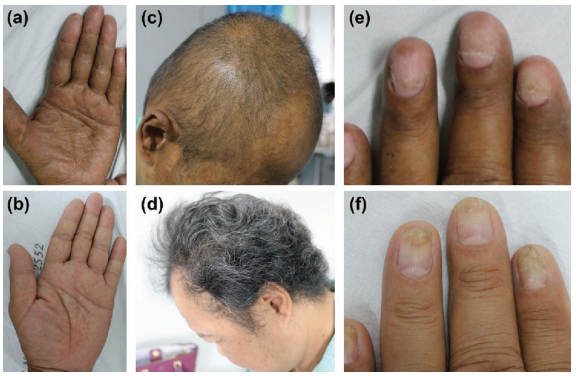

Figure 4. Comparative dermatologic findings before and 6 months after treatment in case number 1. (a) Hyperpigmentation on left palm before treatment. (b) Hyperpigmentation on left palm after treatment. (c) Generalized non-scarring alopecia before treatment. (d) Hair regrowth after treatment. (e) Onychodystrophy before treatment. (f) Normal nail plate regrowth after treatment.

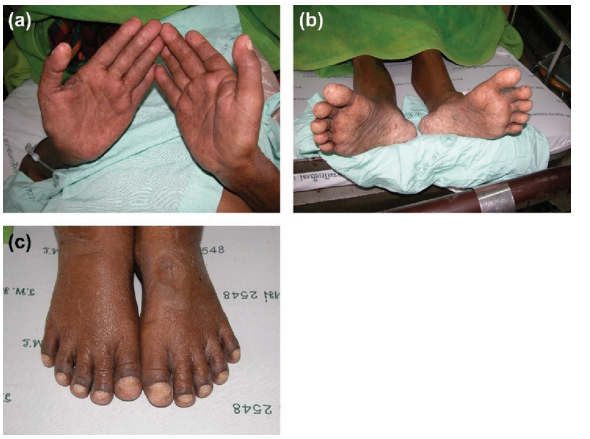

Figure 5. Dermatologic findings in case number 2. (a) Hyperpigmentation on both palms. (b) Hyperpigmentation on both soles. (c) Onychodystrophy of all toenails.

ethnic groups, where alopecia was the most common cutaneous finding, whereas hyperpigmentation was the least common finding among the cutaneous triad. Most of the polyps from Thai patients were hyperplastic and adenomatous polyps, in contrast to the hamartomatous and inflammatory polyps that were more common in other case series.

The pathogenesis of CCS is still being debated. Boland et al demonstrated PRKDC, protein kinase DNA-activated catalytic polypeptide DNA variants from whole-exome analysis of one CCS patient. This finding suggested that genetics may play a role in the pathogenesis of CCS[5]. However, other studies have not supported the theory of familial predisposition[6].

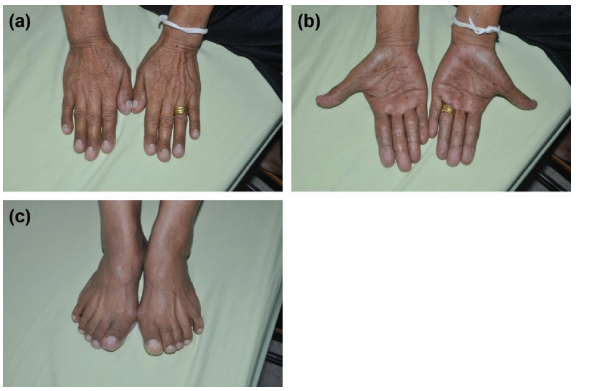

Figure 6. Dermatologic findings in case number 3. (a) Hyperpigmentation on both palms. (b) Onychodystrophy of all fingernails. (c) Onychodystrophy of all toenails.

Table 1. Summary of clinical information of our three study cases and the previously reported Thai patient

	Case 1	Case 2	Case 3	Previously reported Thai patient
Sex, age (years)	Male, 53	Male, 58	Female, 59	Male, 36
Presenting symptoms	Chronic diarrhea, hypogeusia	Chronic diarrhea	Chronic diarrhea	Chronic diarrhea
Cutaneous manifestations	Onychodystrophy Hyperpigmentation of palms and soles Alopecia	Onychodystrophy Hyperpigmentation of palms and soles	Onychodystrophy Hyperpigmentation of palms and soles	Onychodystrophy Hyperpigmentation of palms and soles Alopecia
Gastrointestinal involvement	Hamartomatous polyposis of stomach, duodenum, terminal ileum, colon and rectum	Numerous small hyperplastic polyps in stomach, duodenum, proximal jejunum Numerous adenomatous polyps in the colon	Multiple hyperplastic polyps 0.5 to 1 cm in stomach, duodenum, terminal ileum and colon	Multiple adenomatous polyps along stomach and colon with thickening of the wall of small bowel
Treatment	Oral prednisolone and azathioprine	Total proctocolectomy with ileostomy	NA (patient was referred to another hospital)	Oral prednisolone

NA = not applicable

CCS may be an autoimmune mechanism, with one study reporting that CCS polyps showed IgG4 antibody staining at a significantly higher level than other diseased and normal control tissues[7]. However, IgG4 immunohistochemistry staining of the polyp in one patient in our study showed only slight staining. Some studies reported positive incidence of circulating antinuclear antibodies and anti-Saccharomyces cerevisiae antibodies[8]. To add weight to the autoimmune theory, most cases of CSS had an excellent response to immunosuppressive drugs[7]. Kato et al has proposed Helicobacter pylori infection as one of the causative factors[9]. A few studies reported that mental stress and psychiatric disorders could be precipitating factors. One of our patients responded well to immunosuppressive drugs, both GI symptoms and cutaneous abnormalities showing improvement, supporting the immunopathogenesis of this syndrome.

GI symptoms in CCS patients varied, including diarrhea, abdominal pain, weight loss, nausea, anorexia, hematochezia, vomiting, hypogeusia, and dysgeusia. The characteristic endoscopic findings were inflammatory, non-neoplastic polyps, which could be found throughout the entire GI tract except in the esophagus[10]. However, CCS-associated hamartomatous polyps may look histologically identical to juvenile polyps or gastric hyperplastic polyps. The intervening non-polypoid mucosa in CCS typically shows pathologic changes such as edema, cystically dilated glands, and increased inflammatory cells while the non-polypoid mucosa of juvenile polyposis usually reveals no significant pathologic change[11]. In contrast to gastric hyperplastic polyps, CCS-associated polyps do not reveal prominent inflammation or muscularis hyperplasia[12]. Riegert-Johnson et al suggested that IgG4 immunohistochemistry staining of GI hamartomatous polyps could be helpful in establishing a correct diagnosis of CCS[13]. However, the accurate diagnosis of CCS-associated polyps should not rely on histologic examination alone, but also requires the presence of distinct ectodermal abnormalities[14].

Dermatologically, the characteristic triad of cutaneous manifestations in CCS comprises of onychodystrophy, skin hyperpigmentation, and hair loss[1]. Onychodystrophy, including nail thinning, nail splitting, onycholysis, and onychomadesis, has been found in 98% of patients[15]. Nails with a thin and soft triangular area in the proximal half, bordered by a thick and ridged nail plate, is the typical nail change in CCS patients[16]. This finding was found in all of the authors' patients.

Skin hyperpigmentation, found in 87% of CCS patients, presents as light- to dark-brown macules, predominantly found on the face, neck, palms, and soles[17]. The hyperpigmented skin results from increased melanin with or without an increased number of melanocytes. Electron microscopic findings from involved skin have revealed an increased number of mature melanosomes and melanin granules in melanocytes, together with increased numbers of individually dispersed melanin granules per keratinocyte[17].

Lastly, hair loss in CCS patients begins with a focal area, and could progress to diffuse alopecia involving the entire scalp as well as body hair[18]. Telogen effluvium [TE], triggered by malnutrition, is believed to be the main mechanism[19,20]. However, some studies have found a decrease in hair follicle numbers along with miniaturized or atrophic hair follicles that were not consistent with TE. The timing of the biopsies may account for these different findings, with earlier biopsies compatible with TE that might result from the illness and associated malnutrition.

Corticosteroids are the mainstay of medical treatment for CCS patients. Other reported successful treatments have included aggressive nutritional support, antibiotics, histamine receptor antagonists, cromolyn sodium, non-steroidal anti-inflammatory drugs, immunosuppressive drugs, a tumor necrosis factor inhibitor, and surgery[5,21].

Conclusion

The present study is the first case series of Thai CCS patients. A summary and comparison of the epidemiologic and clinical information from different countries, including the four cases from Thailand are presented. There were frequency differences in each cutaneous finding and the histologic type of the polyps among Thai patients and other ethnic groups.

What is already known on this topic?

CCS presents with GI polyposis and a triad of cutaneous abnormalities including nail dystrophy, alopecia, and hyperpigmentation of the skin. Most of the cases are found in Europeans and Asians, and rarely reported in Thais.

What this study adds?

The authors report the first case series of CCS patients from Thailand and have compared the epidemiologic and clinical information of Thai patients with patients from other countries. The authors found

Table 2. Summary and comparison of epidemiologic and clinical information from 5 case series of different ethnicity

	Goto et al.[22]	Daniel et al.[23]	Qiang et al.[24]	Yun et al.[25]	4 cases from Thailand*
Number of cases	110	55	49	13	4
Average age (years)	NA (most patients were in their fifties)	59	58.3	61.2	51.5
Ethnicity					
Japanese	100%	45.5%	-	-	-
Chinese	-	-	100%	-	-
European	-	54.5%	-	-	-
Korean	-	-	-	100%	-
Thai	-	-	-	-	100%
Male:female ratio	2:1	1.3:1	2:1	1.6:1	3:1
Symptoms					
Diarrhea	84% (most frequent)	92.0%	83.7%	NA	100%
Weight loss	NA	100%	59.2%	NA	-
Abdominal pain	NA	80.0%	57.1%	NA	-
Abdominal distention	-	-	22.4%	NA	-
Weakness	-	91.3%	24.5%	NA	-
Anorexia	NA	83.3%	51.0%	NA	-
Gastrointestinal hemorrhage	NA	76.5%	20.5%	NA	-
Vomiting	-	76.9%	-	NA	-
Hypogeusia	NA	76.9%	-	NA	25%
Paresthesia	NA	66.7%	10.2%	NA	-
Xerostomia	NA	66.7%	-	NA	-
Cutaneous findings					
Hair loss	Nearly 100%	98.0%	91.8%	NA	50%
Nail change	91%	94.4%	98.0%	NA	100%
Hyperpigmentation	79%	86.5%	85.7%	NA	100%
Histopathology of polyps					
Inflammatory polyp	-	-	43.1%	76.9%	-
Hamartomatous polyp	100%	100%	-	7.7%	25%
Hyperplastic polyp	-	-	32.0%	-	50%
Adenomatous polyp	-	-	19.4%	23.1%#	50%
Malignant epithelial polyp	-	-	5.5%	-	-

NA = not applicable

* Comprised of the 3 cases in this case series and the one previous case report[3]

7.7% had carcinoma in situ or high-grade dysplasia

that skin hyperpigmentation was more common in the Thai cases, whereas alopecia was less common when compared to other ethnic groups. The GI polyps of Thai patients were mostly hyperplastic and adenomatous polyps, in contrast to the hamartomatous and inflammatory polyps predominated in other case series.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Cronkhite LW, Jr, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Engl J Med 1955;252:1011-5.
2. Zhao R, Huang M, Banafea O, Zhao J, Cheng L, Zou K, et al. Cronkhite-Canada syndrome: a rare case report and literature review. BMC Gastroenterol 2016;16:23.
3. Viranuvatti V, Damrongsak C, Chainuvati T, Vanasin B, Chandrcharoensin C. Cronkhite Canada syndrome: report of a case with spontaneous recovery. J Med Assoc Thai 1981;64:261-6.
4. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 2003;38:982-4.
5. Boland BS, Bagi P, Valasek MA, Chang JT, Bustamante R, Madlensky L, et al. Cronkhite Canada Syndrome: Significant Response to Infliximab and a Possible Clue to Pathogenesis. Am J Gastroenterol 2016;111:746-8.
6. Chakrabarti S. Cronkhite-Canada Syndrome (CCS)-A Rare Case Report. J Clin Diagn Res 2015;9:OD08-9.
7. Sweetser S, Ahlquist DA, Osborn NK, Sanderson SO, Smyrk TC, Chari ST, et al. Clinicopathologic

features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. Dig Dis Sci 2012;57:496-502.
8. Wen XH, Wang L, Wang YX, Qian JM. Cronkhite-Canada syndrome: report of six cases and review of literature. World J Gastroenterol 2014;20:7518-22.
9. Kato K, Ishii Y, Mazaki T, Uehara T, Nakamura H, Kikuchi H, et al. Spontaneous Regression of Polyposis following Abdominal Colectomy and Helicobacter pylori Eradication for Cronkhite-Canada Syndrome. Case Rep Gastroenterol 2013; 7:140-6.
10. Wijekoon N, Samarasinghe M, Dalpatadu U, Nuzair N, Pratheepan P, Samarasekera D. Proctocolectomy for persistent haematochezia in a patient with Cronkhite-Canada Syndrome. J Surg Case Rep 2012;2012:6.
11. Hornick JL, Odze RD. Polyps of the large intestine. In: Odze RD, Goldblum J, editors. Surgical Pathology of the GI tract, Liver, Biliary Tract, and Pancreas. Philadelphia: Elsevier; 2009. p.481-533.
12. Turner JR, Odze RD. Polyps of the stomach. In: Odze RD, Goldblum J, editors. Surgical Pathology of the GI tract, Liver, Biliary Tract, and Pancreas. Philadelphia: Elsevier; 2009. p.415-45.
13. Riegert-Johnson DL, Osborn N, Smyrk T, Boardman LA. Cronkhite-Canada syndrome hamartomatous polyps are infiltrated with IgG4 plasma cells. Digestion 2007;75:96-7.
14. Burke AP, Sobin LH. The pathology of Cronkhite-Canada polyps. A comparison to juvenile polyposis. The American journal of surgical pathology 1989;13:940-6.
15. Shah KR, Boland CR, Patel M, Thrash B, Menter A. Cutaneous manifestations of gastrointestinal disease: part I. J Am Acad Dermatol 2013;68:189 e1-21; quiz 210.
16. Piraccini BM, Rech G, Sisti A, Bellavista S. Twenty nail onychomadesis: an unusual finding in Cronkhite-Canada syndrome. J Am Acad Dermatol 2010;63:172-4.
17. Herzberg AJ, Kaplan DL. Cronkhite-Canada syndrome. Light and electron microscopy of the cutaneous pigmentary abnormalities. Int J Dermatol 1990;29:121-5.
18. Rahvar M, Kerstetter J. Cutaneous manifestation of gastrointestinal disease. J Gastrointest Oncol 2016;7:S44-54.
19. Allbritton J, Simmons-O'Brien E, Hutcheons D, Whitmore SE. Cronkhite-Canada syndrome: report of two cases, biopsy findings in the associated alopecia, and a new treatment option. Cutis 1998;61:229-32.
20. Watanabe-Okada E, Inazumi T, Matsukawa H, Ohyama M. Histopathological insights into hair loss in Cronkhite-Canada syndrome: diffuse anagen-telogen conversion precedes clinical hair loss progression. Australas J Dermatol 2014;55: 145-8.
21. Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: the many faces of an enigmatic disease. J Clin Pathol 2014;67:891-7.
22. Goto A. Cronkhite-Canada syndrome: epidemiological study of 110 cases reported in Japan. Nihon Geka Hokan 1995;64:3-14.
23. Daniel ES, Ludwig SL, Lewin KJ, Ruprecht RM, Rajacich GM, Schwabe AD. The Cronkhite-Canada Syndrome. An analysis of clinical and pathologic features and therapy in 55 patients. Medicine (Baltimore) 1982;61:293-309.
24. She Q, Jiang JX, Si XM, Tian XY, Shi RH, Zhang GX. A severe course of Cronkhite-Canada syndrome and the review of clinical features and therapy in 49 Chinese patients. Turk J Gastroenterol 2013;24:277-85.
25. Yun SH, Cho JW, Kim JW, Kim JK, Park MS, Lee NE, et al. Cronkhite-Canada syndrome associated with serrated adenoma and malignant polyp: a case report and a literature review of 13 cronkhite-Canada syndrome cases in Korea. Clin Endosc 2013;46:301-5.