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Dear Editors and Reviewers:

Thank you for your letter an for the reviewers' comments concerning our manuscript entitled "Cronkhite-Canada Syndrome with Steroid Dependency： A Case Report" (NO: 61599). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researcher. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are as following:

Responds to the reviewer's comments:

Response to comment (Reviewer#1): (But I if can make a suggestion, I would expand the therapeutic options available nowadays for CCS: because your patient was treated twice with prednisone but it could be interesting for us to know how better options are available.)

Response: Considering the Reviewer's suggestion, we expand the therapeutic schemes available nowadays for CCS and enumerate some specific drug regimen. We have added six references. As following, "Steroid-sparing therapies such as cyclosporine A and an anti-TNF-a agent, a combination that has shown promise in a few cases, can be used in steroid-resistant cases to induce or maintain clinical remission, and other case reports described the beneficial response of immunosuppressive therapies: infliximab, sirolimus, tacrolimus, methicillin, and mycophenolate mofetil [2, 10-14]. Azathioprine and mesalazine used with steroid maintenance therapy were reported to be associated with sustained clinical remission [3, 15-17]. In a study by Eric J. Mao et al. [17], the patient was given a dose

of 1.25 mg/kg/d azathioprine (the previous literature specified a dose of 2 mg/kg/d). The prednisone was tapered off after 6 weeks of therapy, and azathioprine was initiated. Corticosteroid side effects resolved when the prednisone was tapered, and CCS symptoms remained controlled on azathioprine without adverse effects; the total course of treatment consisted of 6 weeks of prednisone and 26 weeks of azathioprine. In a study by Sigrid Schulte et al. [3], discontinuation of steroid therapy was not possible, and mesalazine (1000 mg t.i.d.) was added to prednisolone (10.0 mg/d). The steroid dosage was further reduced over the course of three years; when all polyps had disappeared and the steroid therapy was finished, the dosage of mesalazine was reduced in a stepwise fashion. Four years later, the mesalazine was stopped, and more than 14.0 years after the initial diagnosis, the patient was still in complete remission without any treatment." (page 6 lines 23 to page 7 lines 15)

"**REFERENCES**

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11 Yamakawa K, Yoshino T, Watanabe K, Kawano K, Kurita A, Matsuzaki N, Yuba Y, Yazumi S. Effectiveness of cyclosporine as a treatment for steroid-resistant Cronkhite-Canada syndrome; two case reports. BMC Gastroenterol 2016; 16: 123 [PMID: 27716071 DOI: 10.1186/S12876-016-0541-1]

12 Langevin C, Chapdelaine H, Picard JM, Poitras P, Leduc R. Sirolimus in Refractory Cronkhite-Canada Syndrome and Focus on Standard Treatment. J Investig Med High Impact Case Rep 2018; 6: 2324709618765893 [PMID: 29619395 DOI: 10.1177/2324709618765893]

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14 Liu Y, Zhang L, Yang Y, Peng T. Cronkhite-Canada syndrome: report of a rare case and review of the literature. J Int Med Res 2020; 48: 300060520922427 [PMID: 32459145 DOI: 10.1177/0300060520922427]

15 Takakura M, Adachi H, Tsuchihashi N, Miyazaki E, Yoshioka Y, Yoshida K. A case of Cronkhite-Canada syndrome markedly improved with mesalazine therapy. Dig Endosc 2004; 16: 74-78 [DOI: 10.1111/j.1443-1661.2004.00306.x]"

Special thanks to you for your good comments.

Other changes:

1. The address of the author and corresponding author has been corrected, from "Guangxi" to "Guangxi Zhuang Autonomous Region".

2. We added some "BACKGROUND" information with "The lethality of CCS can be up to 50% if it is untreated or if treatment is delayed or inadequate. More than 35% of the patients didn't achieve long-term clinical remission after corticosteroid administration, which the relapse occurred during or after the cessation of glucocorticoid use. "(page1 lines 25 to 28)

3. We added some "CASE SUMMARY" information with "And then the patient was given 5 mg of prednisone per day for six months of maintenance therapy. With clinical improvement and polyp regression, prednisone was discontinued." (page2 lines 10 to 12)

4. We added some "CONCLUSION" information with "Surveillance endoscopy at intervals of one year or less is recommended to assess mucosal disease activity." (page2 lines 20 to 21)

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5. We added some "**Core tip**" information with "Surveillance endoscopy at intervals of one year or less is recommended to assess mucosal disease activity." (page3 lines 2 to 3)

6. We provided decomposable Figures (whose parts are all movable and editable), organize them into a single PowerPoint file, and submit as "61599-Figures.ppt" on the system.

7. We have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016). We submitted it as "61599-CARE Checklist–2016" on the system.

8. We have redone the English language editing and provided the Non-Native Speakers of English Editing Certificate.

9. The 15th reference has no PMID number, and we have attached the full text below.

"15 **Takakura M,** Adachi H, Tsuchihashi N, Miyazaki E, Yoshioka Y, Yoshida K. A case of Cronkhite-Canada syndrome markedly improved with mesalazine therapy. *Dig Endosc* 2004; 16: 74-78 [PMID: DOI： 10.1111/j.1443-1661.2004.00306.x] " (Appendix A for details)

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Thank you and best regards.

Yours sincerely,

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Appendix A :

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Digestive Endoscopy (2004) 16, 74–78

CASE REPORT

A CASE OF CRONKHITE–CANADA SYNDROME MARKEDLY IMPROVED WITH MESALAZINE THERAPY

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We report a 50-year-old Japanese woman with typical clinical manifestations of Cronkhite–Canada Syndrome (CCS) and possible novel treatment modality for this disease. The patient was diagnosed as CCS based on the presence of several clinical manifestations, such as a diffuse alopecia, nail deformities, hypogeusia, pigmentation of skin, and abdominal discomfort combined with diarrhea and wasting. In addition, she also had multiple polypoid lesions in the gastrointestinal (GI) tract. She was first treated with hyperalimentation and corticosteroid. While this combination therapy seemed to reduce several clinical manifestations, abdominal symptoms and diarrhea recurred with the beginning of oral nutrition. Endoscopy and histology showed that inflammatory changes remained, especially in the lower intestine. Therefore, mesalazine was started. A few days after this therapy, her clinical symptoms disappeared and the polypoid lesions in the large bowel completely resolved. It was therefore possible to restart oral nutrition. We predict that the administration of mesalazine might be one of the useful therapies for CCS.

Key words: Cronkhite–Canada Syndrome, mesalazine.

INTRODUCTION

Cronkhite–Canada Syndrome (CCS), first described by Cronkhite and Canada in 1955,[1] has multiple clinical manifestations, such as gastrointestinal (GI) polyposis associated with diarrhea, and ectodermal changes including alopecia, onychodystrophia, hypogeusia and pigmentation. Since then, 467cases has been reported until the end of 2002 in the world literature. Among them, 354 cases were reported by Japanese groups. Whereas many treatment modalities for CCS have been reported, we often have difficulty in the treatment of many patients with this syndrome. In the present study we report the effect of mesalazine in the treatment of CCS.

CASE REPORT

The patient is a 50-year-old Japanese woman. She is a medical doctor and has been under severe mental stress, in particular for the past 2 years. She first noted hypogeusia, the swelling of the tongue, abdominal pain, and watery diarrhea (10–15 times/day) in February 2002. The loss of hair, eyebrows, axillary and genital hair followed in the next 2 weeks. Pigmentation of the fingers, and thinning of the fingernails followed in March. In addition, she had lost approximately 4 kg in a month. She was admitted to Shiseikai-daini Hospital on 18 March 2002. Her family and medical histories were unremarkable.

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On physical examination, vital signs were within normal ranges. A 10% weight loss from her ideal body weight was indicated. Her scalp revealed alopecia (Fig. 1a). Eyebrows, axillary hair and genital hair were lost. The edge of her tongue was swollen with loss of papilla (Fig. 1b). Fingers showed pigmentation. Fingernails and toenails revealed marked onychodystrophy, and the nail palette were partly exfoliated (Fig. 1c). Tenderness in the epigastrium was remarkable.

Her laboratory data are summarized in Table 1. In brief, hemoglobin concentration was 14.6 g/dL and white blood cell count was 3400/mm^3. Total protein level was 5.2 g/dL, with 3.2 g/dL serum albumin. Cholinesterase was decreased to 0.55ΔPh, suggesting malnutrition. Liver, pancreas and kidney function tests were normal. Potassium levels decreased to 3.1 mEq/L. Urinary protein was negative. A stool specimen was positive for occult blood. Serum tests including immunoglobulin, copper, zinc, and iron, and hormone studies of thyroid, and adrenal gland all revealed almost normal findings. To elucidate her GI function, the following absorption tests were performed. A GI clearance of α1-antitrypsin was elevated at 57.8 mL/day (normal range < 13 mL/day). A D-xylose absorption test decreased to 0.5 g/5 h. Sudan III stain was positive. Scintigraphy using a technetium-99m-labeled human albumin demonstrated the leakage to the GI tract.

An upper GI endoscopy showed red carpet-like polyposis on edematous mucosa throughout the stomach and duodenum (Fig. 2a). Colonoscopy revealed small sessile polyposis from the terminal ileum to the rectum (Fig. 3a). A biopsy specimen demonstrated pit distortion and dilatation, and severe edema was recognized in the thickened stroma of the lamina propria associated with inflammatory cells. Pit abscesses indicated evidence of acute severe inflammation

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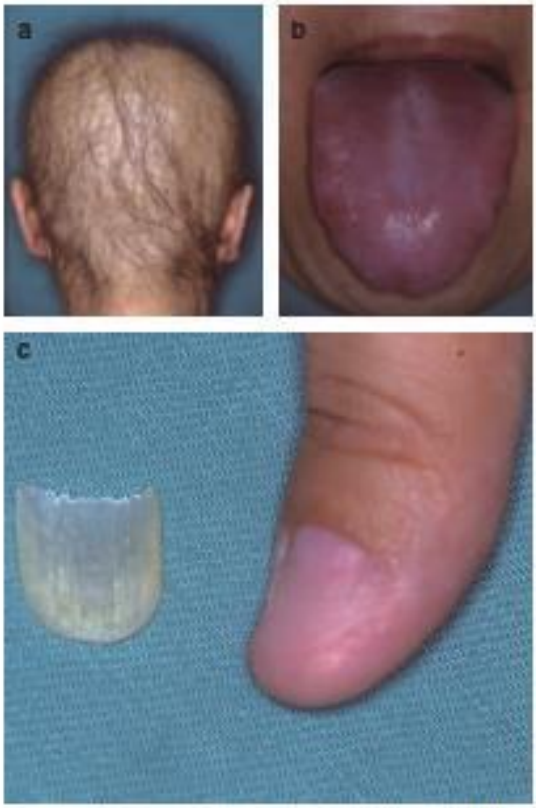

Fig. 1. Ectodermal changes before any treatments. (a) Diffuse alopecia; (b) changes of the tongue, swelling with loss of papilla; (c) exfoliated fingernail.

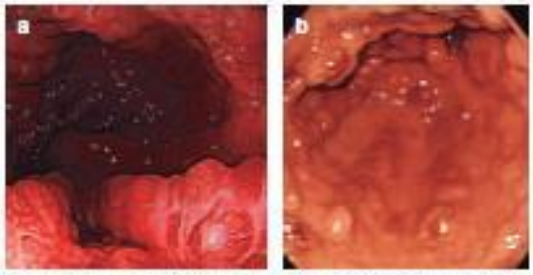

Fig. 2. Upper gastrointestinal (GI) endoscopy. (a) Before treatment: red carpet-like polyposis on adenomatous mucosa in the stomach. (b) After corticosteroid and mesalazine therapy: some polyposis remaining in the stomach.

(Fig. 4a). A biopsy specimen from the terminal ileum demonstrated mildly edematous stroma with inflammatory cell infiltration containing neutrophils with focal erosive change (Fig. 4c). A biopsy specimen from the colonic mucosa demonstrated crypt distortion and dilatation resembling the change in the stomach. Thick inflammatory cells composed of lymphocytes had infiltrated the stroma of the lamina propria. Also, crypt abscesses were indicated (Fig. 4d). These features, both of endoscopic and histological examinations, are compatible with the classic ectodermal changes of CCS. Further examinations of the small intestine were not performed, due to the patient's refusal.

After admission, intravenous transfusion of prednisolone (PSL) was initiated at a daily dose of 30 mg together with hyperalimentation. She initially responded well to this combination therapy. The frequency of diarrhea decreased to five times or less each day, and her bodyweight gradually recovered. Hypogeusia, alopecia and deformities of the fingernails also resolved. After PSL was then tapered to 25 mg daily, elemental diet (ED) therapy (80 g daily) was started. With

Table 1. Laboratory data on admission

Urinary test		Blood chemistry		Hormone	
Protein	(–)	TP	5.2 g/dL	TSH	0.3 μIU/mL
Glucose	(–)	Alb	3.3 g/dL	fT3	3.2 pg/mL
Stool test		T-bil	0.6 mg/dL	fT4	1.4 ng/dL
Occult blood	(+)	AST	21 IU/L	ACTH	19.9 pg/mL
Sudan III	(+)	ALT	16 IU/L	Cortisol	26.8 μg/dL
		Ch-E	0.55 ΔPh	17-OHCS	0.71 mg/dL
		BUN	4.9 mg/dL	Gastrin	135 pg/mL
Blood analysis		Cr	0.4 mg/dL	Immune test	
WBC	3400/mm³	Na	141 mEq/L	IgG	700 mg/dL
RBC	434 × 10⁴/mm³	K	3.1 mEq/dL	IgA	138 mg/dL
Hb	14.6 g/dL	Cl	106 mEq/dL	IgM	55 mg/dL
Ht	41.7%	Fe	192 μg/dL	CH50	41 IU/mL
Plt	17.5 × 10⁴/mm³	Cu	98 μg/dL	C3	94 mg/dL
ESR 1'	5 mm	Zn	81 μg/dL	C4	29.2 mg/dL
		CRP	0.3 mg/dL	ANA	< 40
				DNA	< 80
		Tumor marker		Absorption test	
		CEA	1.2 ng/mL	α1-antitrypsin	57.8 mL/day
		CA 19-9	8.8 U/mL	D-xylose	0.5 g/5 h

ALT, alanine aminotransferase; AST, aspartate transferase; BUN, blood urea nitrogen; CRP, C-reactive protein; CEA, carcinoembryonic antigen.