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【 CASE REPORT 】

Recombinant Thrombomodulin Used to Successfully Treat Cronkhite-Canada Syndrome with Disseminated Intravascular Coagulation due to Sepsis in a Compromised Patient

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Abstract:
Cronkhite-Canada syndrome (CCS) is a rare non-inherited disease characterized by gastrointestinal polyposis, chronic diarrhea, ectodermal dysplasia, skin hyperpigmentation, hair loss and nail atrophy. Although the efficacy of corticosteroid and immunomodulatory agents has been demonstrated, no standard therapy regimen has been established, and the prognosis of CCS is still poor due to various complications. We here in report a CCS patient complicated with severe sepsis and disseminated intravascular coagulation who was successfully treated by combined modality therapies, including recombinant human soluble thrombomodulin.

Key words: bacterial translocation, Cronkhite-Canada syndrome, disseminated intravascular coagulation, gastrointestinal polyposis, recombinant human soluble thrombomodulin, sepsis

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Introduction

Cronkhite-Canada syndrome (CCS) is a rare nonfamilial gastrointestinal polyposis syndrome first reported by Cronkhite and Canada in 1955 (1). CCS is characterized by the presence of diffused gastrointestinal polyposis, chronic diarrhea, ectodermal dysplasia, skin hyperpigmentation, hair loss and nail atrophy. The diagnosis of CCS is based on the patient's history, physical examination findings and endoscopic and histopathological findings. Corticosteroids, dietary supplementation, immunomodulatory agents, salazosulfapyridine, anti-tumor necrosis factor antibody and antibiotics have shown some efficacy (2); however, a standard therapy regimen has yet to be established. Although corticosteroids appear to be the most effective treatment so far, they can increase the risk of severe infection. Therefore, the prognosis of CCS is still poor.

It was reported that the 5-year mortality rate exceeded 50% (3). Given these circumstances, the clarification of the short- and long-term clinical course of CCS and the development of effective therapeutics are very important. Recently, recombinant human soluble thrombomodulin (rTM) has been reported to improve the prognosis of patients with sepsis-induced disseminated intravascular coagulation (DIC) (4). However, the effectiveness of rTM in treating the complications of CCS has not been established.

We here in report a patient with CCS who developed severe gastrointestinal infection, bacterial translocation, sepsis and DIC and was successfully treated with combined modality therapies including rTM.

Case Report

A 64-year-old man was admitted to our hospital because of diarrhea, severe edema, hypoalbuminemia and gastrointestinal polyposis. He had been diagnosed with colon cancer and had received curative resection of colon cancer at another hospital seven months earlier. At that time, gastrointestinal polyposis had not been detected by an endoscopic examination. Two months after the operation, he began to suffer from diarrhea, dysgeusia and dystrophic changes in his

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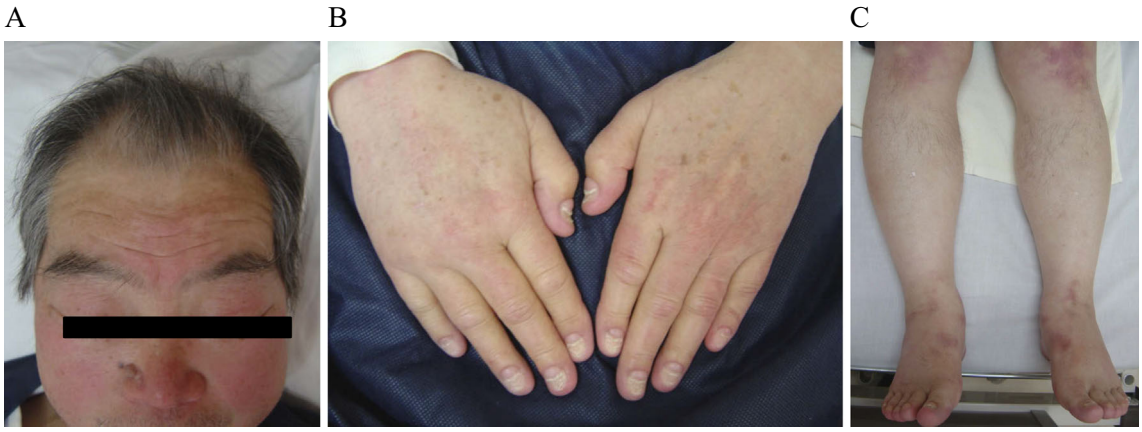

Figure 1. **Physical findings of the patient on admission. Alopecia (A), onychodystrophy (B) and severe edema of both legs (C) were seen.**

Table. **Laboratory Data of the Patient on Admission.**

Hematology					
WBC	7,400 /μL	BUN	27 mg/dL	IgM	25 mg/dL
RBC	441×10⁴ /μL	Cre	1.02 mg/dL	IgG4	21.8 mg/dL
Hb	14.2 g/dL	Na	140 mEq/L		
Hct	40.1 %	K	3.3 mEq/L	Coagulation	
PLT	21.2×10⁴ /μL	Cl	102 mEq/L	PT	98.7 %
		Fe	109 μg/dL	APTT	29.2 sec
Biochemistry		Ferritin	66 ng/mL	Fibrinogen	256 mg/dL
TP	3.2 g/dL	Ca	6.4 mg/dL		
Alb	1.0 g/dL	Mg	298 mg/dL	Tumor markers	
T-Bil	0.3 mg/dL	Cu	53 μg/dL	CEA	14.4 ng/mL
D-Bil	0.1 mg/dL	Zn	30 μg/dL	CA19-9	140.1 U/mL
AST	32 IU/L	Vitamine B_{12}	845 pg/mL		
ALT	32 IU/L	HbA1c	5.2 %	Urine	
LDH	430 IU/L			Ph	6.5
ALP	230 IU/L	Serology		Bil	(-)
γ-GTP	7 IU/L	CRP	7.68 mg/dL	protein	(1+)
TG	96 mg/dL	IgG	397 mg/dL	glucose	(-)
T-Cho	125 mg/dL	IgA	141 mg/dL		

fingernails. He then developed severe general edema and an increase in bodyweight and was admitted to our hospital to determine the cause of the illness.

On admission, his vital signs were as follows: blood pressure of 120/80 mmHg, heart rate of 84 beats per minute and body temperature of 36.5°C. A physical examination showed hair loss, nail changes, skin hyperpigmentation, abdominal swelling, general edema and weak respiratory sounds (Fig. 1). Regarding the laboratory data, the white blood cell (WBC) count, hemoglobin and platelet (PLT) count were within the normal range. Biochemical examinations showed mild renal dysfunction. Serum total protein and albumin levels were markedly decreased. Liver function tests were within normal range. Serum trace elements were below normal. Immunoglobulin levels were very low, while C-reactive protein (CRP) was elevated. Coagulation tests were within the normal range. A urinary examination did not demonstrate proteinuria (Table). Various sizes of polyps with nodular edematous mucosa were found in the stomach and duodenum by esophagogastroduodenoscopy (EGD) (Fig. 2A) and in the colon by colonoscopy (Fig. 2B). An endoscopic examination confirmed diffuse sessile or pedunculated polyps with either a smooth or rough surface (Fig. 2A, B). Histopathological examinations of the polyps revealed hyperplasia of the foveolar epithelium, cystically dilated glands and edematous stroma with mild chronic inflammation (Fig. 2C). Radiology of the gastrointestinal tract showed no polyposis in the small intestine. Contrast-enhanced computed tomography (CT) of the chest and abdomen showed a large quantity of pleural effusion and ascites (Fig. 3A). The ascites was colorless and clear (Fig. 3B). The result of an α-1 antitrypsin clearance test was 284 mL/day (normally under 13 mL/day), indicating protein-losing gastroenteropathy. We diagnosed the patient with protein-losing gastrointestinal disease due to CCS based on his clinical history, physical examination findings, α-1 antitrypsin clearance test results

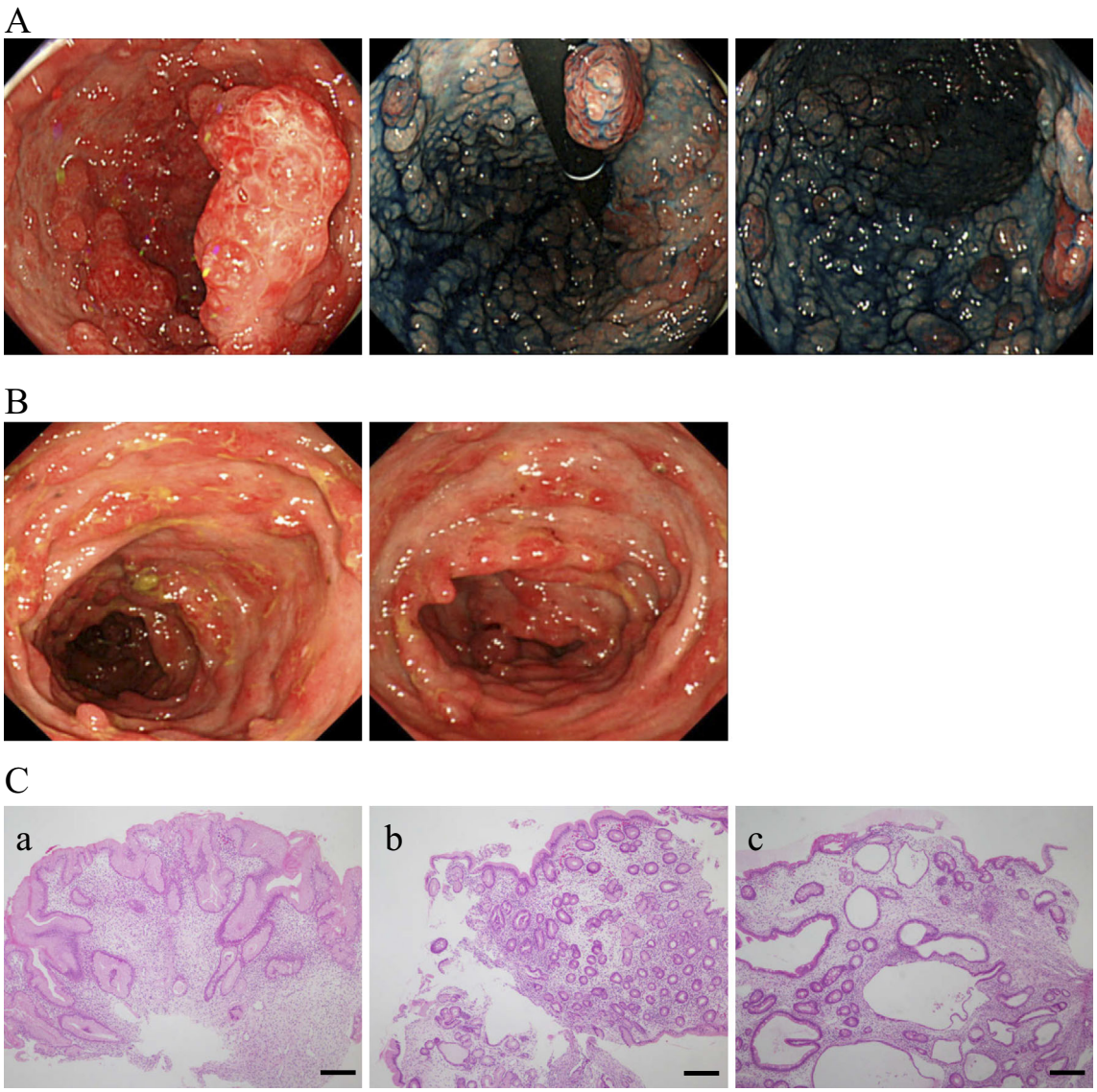

Figure 2. **Endoscopic and histopathological findings. Esophagogastroduodenoscopy (EGD) (A) and colonoscopy (B) of the patient before starting steroid therapy. Numerous polyps occupied the gastroduodenal and colonic mucosa (C). Histopathological findings of the polyps in the stomach (a, b) and duodenum (c) revealed hyperplasia of the foveolar epithelium, cystically dilated glands and edematous stroma with chronic inflammation. Scale bar=200 μm.**

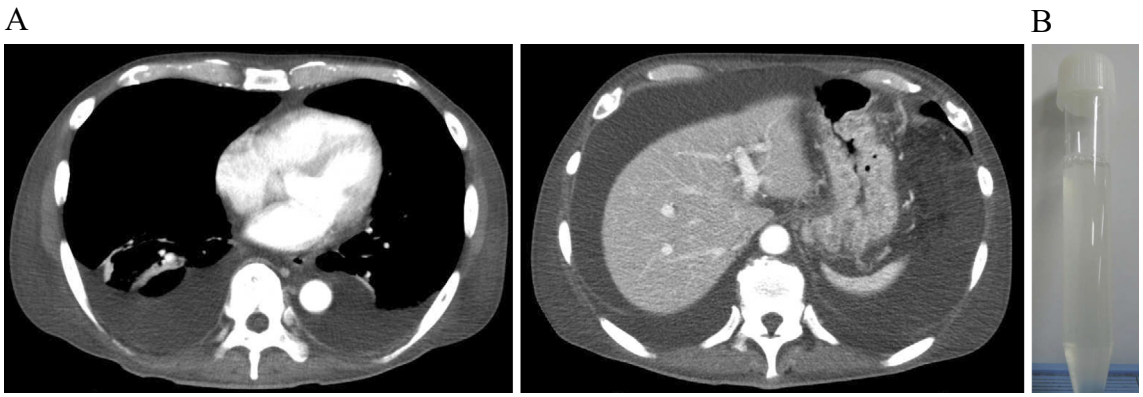

Figure 3. **Contrast-enhanced CT of the chest and abdomen and the appearance of the ascites. Pleural effusion and ascites were seen (A). The ascites was colorless and clear (B).**

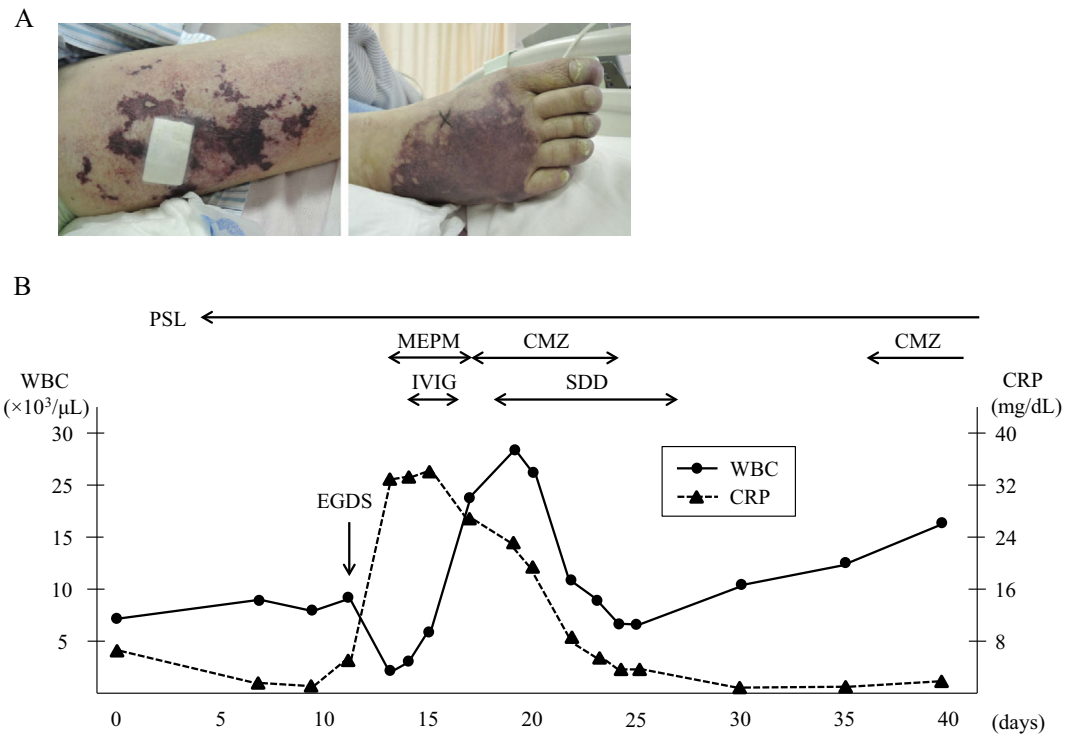

Figure 4. **Skin findings of the left leg showed erythema, swelling and blisters (A). The clinical course of this patient after admission (B). PSL: prednisolone, CMZ: cefmetazole, MEPM: meropenem, IVIG: intravenous immunoglobulin, SDD: selective decontamination of the digestive tract, EGD: esophagogastroduodenoscopy, WBC: white blood cell, CRP: C-reactive protein**

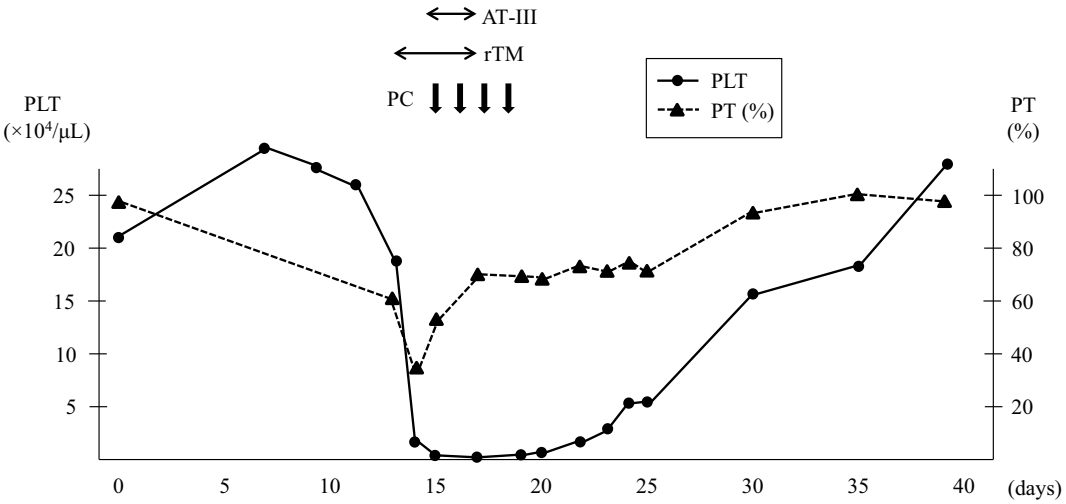

Figure 5. **The clinical course of coagulation disorder in the present case. AT: antithrombin, rTM: recombinant human soluble thrombomodulin, PC: platelet concentrates, PLT: platelet, PT: prothrombin time**

and endoscopic findings of gastrointestinal polyposis.

We treated the patient with prednisolone (PSL) at 1 mg/kg/day (60 mg/day). Because epigastralgia developed eight days after the initiation of the steroid treatment, we performed EGD again. After the examination, his general condition suddenly worsened. His vital signs at that time were as follows: blood pressure of 48/26 mmHg, body temperature of 39.2°C, heart rate of 120/min, respiratory rate of 20/min and SpO_2 of 90% (room air). A physical examination showed a fever, erythema, blisters and swelling of the left thigh (Fig. 4A). *Escherichia coli* was detected in blood cultures and effusion of exudative dermatitis. In addition, his serum endotoxin had risen to 2,294 pg/mL (normally under 1 pg/mL), and procalcitonin, which is considered one of the most telling sepsis markers (5), reached 74 ng/mL (normally under 0.05 ng/mL) at its peak. Therefore, we diagnosed the

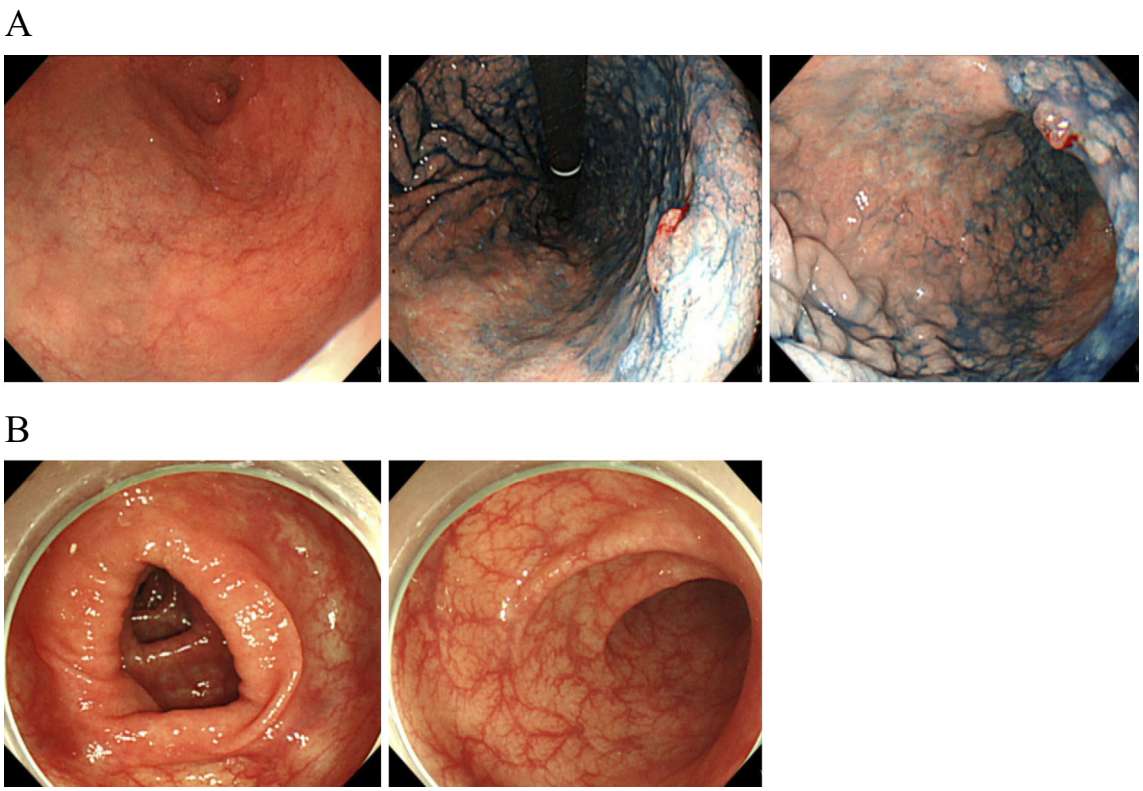

Figure 6. **Esophagogastroduodenoscopy (EGD) (A) and colonoscopy (B) of the patient after the treatment with prednisolone and immunomodulatory agents. The polyps in both the stomach and the colon were improved.**

patient with bacterial translocation due to an increase in gastrointestinal pressure, resulting in septic shock associated with malnutrition, hypogammaglobulinemia and steroid therapy.

We utilized the parameters of the Japanese Association for Acute Medicine (JAAM) DIC criteria (6), including ≥ 3 of the findings of systemic inflammatory response syndrome (SIRS) (body temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or $PaCO_2$ <32 mmHg, WBC > 12,000/mm^3 or <4,000/mm^3), a PLT count ≥80,000/mm^3 and <120,000/mm^3, prothrombin time-international normalized ratio (PT-INR) ≥1.2, fibrinogen degradation product (FDP) ≥ 10 μg/mL and <25 μg/mL. As mentioned above, his vital signs at that time were a body temperature of 39.2°C, heart rate of 120/min, respiratory rate of 20/min, WBC of 900/mm^3, PLT of 88,000/mm^3, PT-INR of 1.9 and FDP of 15.9 μg/mL. With a total score of 6 points, he more than met the criteria. PLT count decreased markedly, reaching as low as 500/μL. Although dissociation was noted between the PT and PT-INR and FDP, we diagnosed him with DIC caused by sepsis. The elevation of the D-dimer level (5.9 μg/mL) and the decrease in the antithrombin (AT)-III activity (35%) supported the diagnosis of DIC.

We immediately started antibiotics, intravenous immunoglobulin (IVIG) and selective decontamination of the digestive tract (SDD) for the severe sepsis. We also started anticoagulant therapy with rTM and AT-III for the DIC. His condition gradually improved after these multimodal treatments, and he recovered from both the septic condition and DIC (Fig. 4B, 5). Two weeks after starting steroid therapy, we gradually tapered the dosage of PSL to 10 mg/day over the following 5 months. Continuing the dose of PSL at 10 mg/day, we started immunomodulatory agents including mesalazine (2,250 mg/day) at 4 months after the initiation of PSL and azathioprine (25 mg/day) at 5 months after the initiation of PSL, as his serum albumin decreased due to tapering of the dosage of PSL. One month later, a repeated α-1 antitrypsin clearance test revealed improvement in his protein-losing gastrointestinal disease (11.6 mL/day), so the treatment with PSL and immunomodulatory agents was continued. Thirteen months after the initiation of the steroid therapy, we gradually tapered the dosage of PSL further to 5 mg/day in combination with immunomodulatory agents. Two years later, an endoscopic examination showed improvement in both his gastric and colorectal polyps (Fig. 6), and the patient appeared to still be in remission for CCS.

Discussion

CCS is a rare nonfamilial gastrointestinal polyposis syndrome characterized by hamartomatouspolyps, protein-losing gastroenteropathy and ectodermal changes with a varied clinical course. Approximately 400 cases of CCS have been reported worldwide, including in Japan (7, 8). Although the etiology of CCS is unclear, previous reports have suggested that autoimmunesystem, infection and mental or physical

stress are probably associated with CCS (9). In the present case, physical stress may have been at least partially correlated with the pathogenesis of CCS, as the symptoms and findings of CCS, including gastrointestinal polyposis and protein-losing gastroenteropathy, emerged after surgical treatment for colon cancer.

In recent years, cases of several cancers complicated with CCS, especially gastric cancer and colorectal cancer, have increased (8, 10). Colon polyposis was not detected at the time of the diagnosis of colon cancer, and we considered that the colon cancer in this patient was not associated with the colon polyposis of CCS in this case. However, one year after the diagnosis of CCS, we performed endoscopic mucosal resection of the polyps, and the histopathological findings revealed adenoma. It will therefore be necessary to monitor the patient carefully with regard to the possible future onset of cancer.

We believe that the most important factor affecting the prognosis of CCS at the initial stage, including the diagnosis and the initiation of treatment, is not malignancy but severe infection (11). Although the optimum treatment has not been established, corticosteroids, dietary supplementation, immunomodulatory agents, salazosulfapyridine, anti-tumor necrosis factor antibody, antibiotics and surgery have shown some efficacy in treating CCS (12). At present, corticosteroids in particular seem to provide the best chance of improving the prognosis in CCS and should therefore be considered the key drug for treating CCS, despite the increased risk of severe infection (13-15). Severe infection is closely related to the condition of the host and to the pathogenic agent. If the immunity of the host is normal, severe infections are rare, and even if they develop, they tend to respond to appropriate treatments.

Opportunistic infections are more likely to occur when the immunity of the host is compromised. It is well known that our immunity is closely tied to the presence of plasma proteins. CCS is a disease associated with hypoproteinemia accompanied by protein leakage. Therefore, this condition may facilitate infection by various pathogens. It has been suggested that bacterial translocation may occur more easily in cases of colitis due to disuse of the gastrointestinal tract (16, 17). The condition of the present patient was compromised by steroid treatment, malnutrition and hypogammaglobulinemia. Therefore, bacterial translocation may have occurred due to the fragility of the gastrointestinal mucosa in CCS and to the endoscopic examination-mediated increase in gastrointestinal pressure. Early multimodal therapy to treat the symptoms of infection is necessary, especially in patients with CCS who receive invasive examinations. In the present case, the CRP level was already elevated at the time of admission, and chronic inflammation of the gastrointestinal tract might already have been present.

According to "The Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3)" announced in February 2016 (18), sepsis is defined as a condition causing an uncontrollable host reaction to infectious diseases accompanied by life-threatening organ failure. DIC develops in critical conditions associated with sepsis and is thought to be a factor associated with a poor prognosis. In the present case, the diagnosis of DIC was based on the JAAM DIC criteria. Although many anti-coagulant therapies have been evaluated, there is no unified view on the usefulness of anti-coagulant therapy in sepsis-induced DIC.

SEPSIS-3 suggests the usefulness of rTM for treating septic DIC, but no clear recommendations have been put forward. In fact, several studies have demonstrated the efficacy of rTM on sepsis-induced DIC (19-21). Treatment with rTM was shown to inhibit activation of inflammatory cytokines induced by endotoxemia (22). In addition, a direct anti-inflammatory effect of rTM has also been demonstrated (23-25). Thus, rTM seems to be more attractive than other conventional anti-coagulation agents in the treatment for sepsis-induced DIC. There have been no reports of CCS cases complicated with DIC. Thus, the appropriate treatment of DIC complicated with CCS has not been established. We consider the administration of rTM to be therapeutically beneficial in sepsis-mediated DIC complicated with CCS patients due to its anti-inflammatory effect and low risk of bleeding complications.

In the present case, *Escherichia coli* was detected in blood cultures and was considered to be the pathogen underlying sepsis and DIC. As mentioned above, rTM has been reported to have anti-inflammatory effects, such as the neutralization of lipopolysaccharides, inhibition of leukocyte adhesion to endothelial cells and compliment pathways, suppression of inflammatory cytokines and degradation of high-mobility group box 1 protein (25). Therefore, rTM administration was considered to be a more appropriate treatment than other conventional anti-DIC agents for septicemia and sepsis-induced DIC in this patient. Furthermore, the existence of gastrointestinal mucosal disorder in CCS may increase the risk of gastrointestinal bleeding under DIC conditions. Therefore, rTM treatment seems to be more effective in treating CCS than other diseases.

We encountered a case in which rTM therapy successfully improved severe sepsis-induced DIC associated with CCS. In addition, the safety of rTM in gastrointestinal polyposis was also shown because the patient did not experience any adverse events associated with rTM treatment, including gastrointestinal bleeding. To our knowledge, this is the first report of the successful treatment with rTM in a patient with DIC associated with CCS.

In conclusion, corticosteroid and immunomodulatory agents are very useful for improving the symptoms and the long-term prognosis of CCS. However, we should monitor patients with CSS carefully for severe infections, especially those receiving immunosuppressive therapy. In cases of CCS with severe sepsis and DIC, rTM is an effective treatment option and may improve the prognosis of CCS. The further accumulation of cases is needed to establish a standard treatment for intractable cases of CCS.

The authors state that they have no Conflict of Interest (COI).

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