CEN Case Reports
https://doi.org/10.1007/s13730-024-00908-9

CASE REPORT

A case of membranous nephropathy complicated by Cronkhite–Canada syndrome successfully treated with mizoribine

Hiroyuki Nakanoh[1] · Kenji Tsuji[1] · Shiho Morimoto[1] · Kazuhiko Fukushima[1] · Masaya Iwamuro[2] · Haruhito A. Uchida[3] · Jun Wada[1]

Received: 29 February 2024 / Accepted: 21 June 2024

Abstract
Cronkhite–Canada syndrome (CCS) is a non-hereditary disorder characterized by non-neoplastic hamartomatous gastrointestinal polyposis, hair loss, nail atrophy, hyperpigmentation, and diarrhea. While the relationship between CCS and nephritis remains unclear, seven cases of nephritis complicated by CCS have been reported to date, all of which were membranous nephropathy (MN). A 57-year-old man presented with taste disturbance, hair loss, nail plate atrophy, skin pigmentation, and frequent diarrhea. Endoscopic findings showed multiple polyposis of the stomach and large intestine. Given the above, he was diagnosed with CCS. The symptoms gradually improved with prednisolone treatment, although urinary protein and hypoproteinemia appeared during the tapering of prednisolone. He was diagnosed with MN using a renal biopsy, and immunofluorescence microscopy with IgG subclass staining showed predominantly diffuse granular capillary wall staining of IgG4. The cause of secondary MN was not found, including malignant tumors. Nephrotic-range proteinuria persisted despite treatment with prednisolone and cyclosporine. Additional treatment with mizoribine resulted in incomplete remission type 1 of nephrotic syndrome, suggesting that mizoribine may be a treatment option for patients with CCS with steroid-resistant MN. Considering a high prevalence of hypoproteinemia due to chronic diarrhea and protein-losing enteropathy in patients with CCS, proteinuria might be overlooked; thus, follow-up urinalysis would be recommended in patients with CCS.

Keywords Cronkhite–Canada syndrome · Membranous nephropathy · Nephrotic syndrome · Mizoribine

Introduction

Cronkhite–Canada syndrome (CCS) is a non-hereditary disorder characterized by non-neoplastic hamartomatous gastrointestinal polyposis, hair loss, nail atrophy, hyperpigmentation, and diarrhea. While the etiology of CCS remains unclear, it has been reported that in CCS, hamartomatous polyps are infiltrated with IgG4 plasma cells; thus, CCS may have an autoimmune background [1]. Indeed, in the literature, CCS has been associated with some autoimmune diseases, including hypothyroidism [2, 3], systemic lupus erythematosus [4], Basedow's disease [5], and type 1 diabetes [6]. Regarding complications of nephritis, there are only seven reports of nephritis accompanied by CCS, all of which have been proven to be membranous nephropathy (MN), but a functional link between CCS and MN has not been demonstrated. Herein, we report a case of MN with CCS. In this case, immunofluorescent staining of the renal biopsy specimen showed that IgG4 was predominantly stained in the IgG subclass.

Case report

A 57-year-old man with CCS was referred to our department because of urinary protein and occult blood. Three years prior to the presentation, he developed dysgeusia, frequent

✉ Kenji Tsuji
ktsuji@s.okayama-u.ac.jp

[1] Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-Cho, Okayama 700-8558, Japan

[2] Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[3] Department of Chronic Kidney Disease and Cardiovascular Disease, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Published online: 02 July 2024

diarrhea, hair loss, nail plate atrophy, and skin pigmentation. The endoscopic examination showed multiple reddish gastrointestinal inflamed areas and adenomatous polyposis (Fig. 1A and B), and the histopathological examination of the polyp specimens revealed a severely edematous stroma, cystic dilated ducts, and mononuclear or neutrophil cell infiltration (Fig. 1E and F) without malignancy. These findings led to the diagnosis of CCS. Immunohistochemical analysis of IgG4 of colon polyp was negative. Prednisolone therapy (30 mg/day) was started to treat CCS; thereafter, the clinical symptoms gradually improved. However, when the prednisolone dose was gradually tapered, the hair loss and nail plate atrophy worsened and urinary protein and occult blood appeared. The patient had a history of pituitary adenoma, hypopituitarism, adrenal insufficiency, central hypothyroidism, symptomatic epilepsy, and atopic dermatitis. There was no family history of gastrointestinal and kidney diseases.

On admission, he was on prednisolone (8 mg/day) for CCS, hydrocortisone (15 mg/day) for hypopituitarism, and levothyroxine sodium (25 µg/day) for central hypothyroidism. The patient's body temperature was 36.6 °C, pulse rate was 84 per minute, and blood pressure was 123/80 mmHg. Pigmentation of the limbs and trunk, vitiligo on the head, and nail plate atrophy were observed (Fig. 1). Lower-leg edema was not observed. The laboratory data on admission are shown in Table 1. The urinalysis showed proteinuria (3 +) quantitated at 3.97 g/gCr and occult blood (±). The blood tests showed low levels of serum total protein (6.0 g/dL), serum albumin (3.2 g/dL), and a normal serum creatinine level (0.88 mg/dL). The chest and abdomen computed tomography (CT) revealed no abnormal findings. Esophagogastroduodenoscopy and colonoscopy revealed multiple polyposis of the stomach and large intestine, but the number of polyps

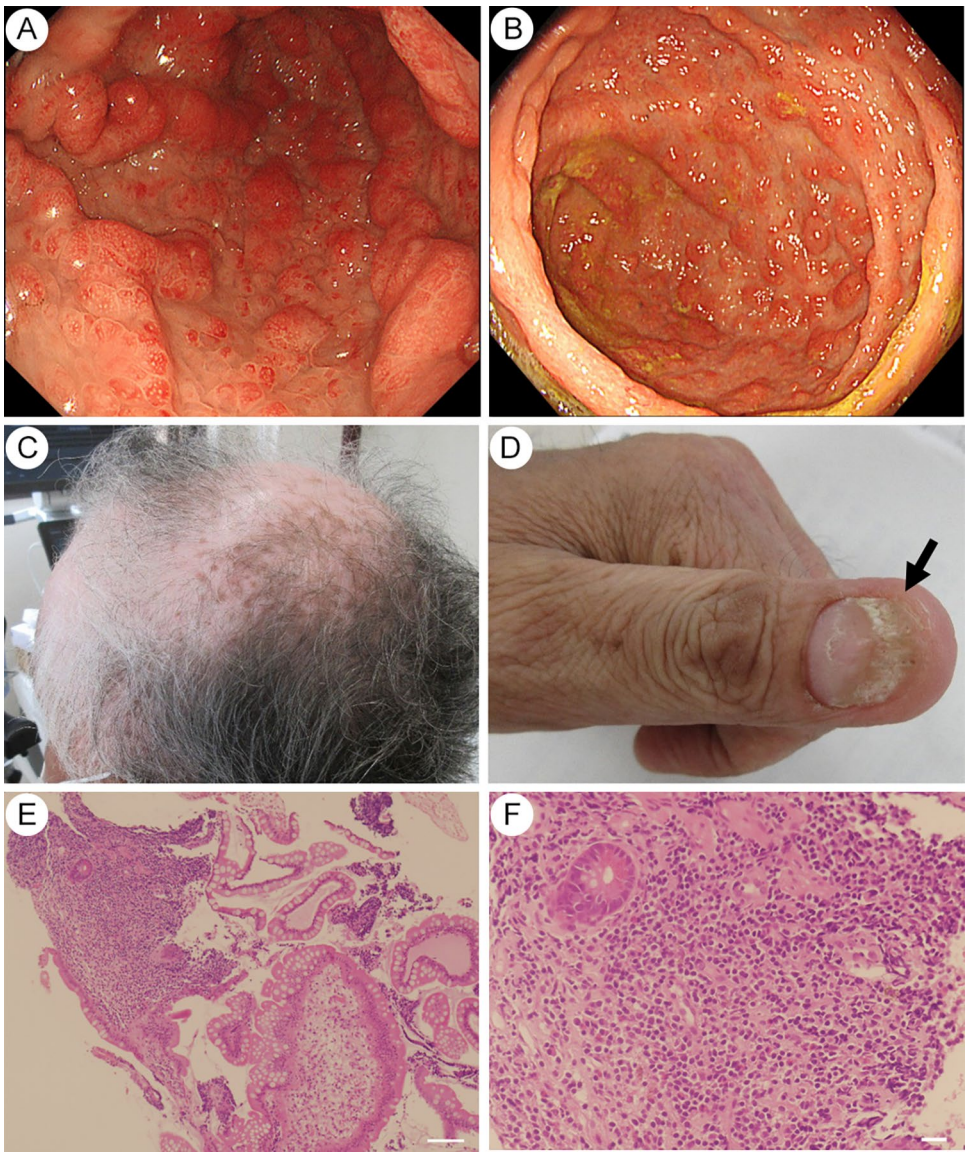

Fig. 1 Findings of CCS. **A** Multiple reddish areas of gastrointestinal inflammation seen via esophagogastroduodenoscopy at the time of CCS diagnosis. **B** Multiple reddish adenomatous polyposis seen via colonoscopy at the time of CSS diagnosis. **C** Head image, showing hair loss, skin pigmentation, and vitiligo. **D** Hand image, showing nail plate atrophies (arrow). **E, F** Hematoxylin and Eosin stain images of colon polyp biopsy specimen, showing inflammatory cell infiltrations, including eosinophils. Scale bars: 100 µm (**E**) and 20 µm (**F**)

Table 1 Laboratory data on admission

Blood cell count	
White blood cell	8700 /μL (3300–8600)
Red blood cell	466 × 104 /μL (435–555)
Hemoglobin	12.3 g/dL (13.7–16.8)
Hematocrit	41.2% (40.7–50.1)
Platelet	44.4 × 104 /μL (15.8–34.8)
Coagulation	
PT	9.8 s
APTT	25.1 s (26.9–38.1)
PT-INR	0.94 (0–2.99)
D-dimer	< 0.5 μg/mL (0–0.9)
Blood chemistry	
Total protein	6.0 g/dL (6.6–8.1)
Albumin	3.2 g/dL (4.1–5.1)
AST	13 IU/L (13–30)
ALT	13 IU/L (10–42)
Uric acid	7.0 mg/dL (3.7–7.8)
BUN	16.0 mg/dL (8.0–20.0)
Cr	0.88 mg/dL (0.65–1.07)
Sodium	140 mEq/L (138–145)
Potassium	3.5 mEq/L (3.6–4.8)
Chloride	107 mEq/L (101–108)
Calcium	9.2 mg/dL (8.8–10.1)
iP	3.8 mg/dL (2.7–4.6)
HbA1c	5.3% (4.9–6.0)
BNP	19.6 pg/mL (0–18.4)
FT4	0.84 ng/dL (0.97–1.69)
TSH	0.57 mIU/L (0.33–4.05)
CRP	0.07 mg/dL (< 0.15)
Immunologic test	
IgG	869.5 mg/dL (861–1747
IgA	361.7 mg/dL (93–393)
IgM	31.9 mg/dL (33–183)
C3	101.8 mg/dL (73–138)
C4	21.3 mg/dL (11–31)
CH50	54 U/mL (32–58)
ANA	< × 40 (< 40)
IgG4	< 14.6 mg/dL (14.6–117)
MPO-ANCA	< 0.2 IU/mL (< 3.50)
PR3-ANCA	< 1.6 IU/mL (< 2.00)
anti-GBM	< 1.5 U/mL (< 6.99)
Anti-RNP	0.88 U/mL (< 3.5)
Anti-SS-A	< 0.40 U/mL (< 7.0)
Anti-dsDNA	< 0.60 IU/mL (< 10.0)
HBs-Ag	Negative
HCV-Ab	Negative
HIV-Ab	Negative
Cryoglobulin	Negative
Urinalysis	
Protein	(3 +)
Occult blood	(±)
Glucose	(−)
Red blood cell	1–4 /HPF
White blood cell	5–9/HPF
U-Protein	3.97 g/gCr
NAG	15.1 U/L (0.3–11.5)
β2MG	1241 μg/mL (< 0.290)

The values in the parentheses show the normal range.

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *BUN* blood urea nitrogen, *Cr* creatinine, *iP* inorganic phosphorus, *HbA1c* hemoglobin A1c, *BNP* brain natriuretic hormone, *FT3* free triiodothyronine 3, *FT4* free triiodothyronine 4, *TSH* thyroid stimulating hormone, *CRP* cross-reactive protein, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *IgM* immunoglobulin M, *C3* complement C3, *C4* complement C4, *CH50* hemolytic complement, *ANA* antinuclear antibody, *MPO-ANCA* myeloperoxidase anti-neutrophil cytoplasmic antibodies, *PR3-ANCA* proteinase3 anti-neutrophil cytoplasmic antibodies, *anti-GBM* anti-glomerular basement membrane antibody, *Anti-RNP* ribonucleoprotein, *Anti-SS-A* Anti-SS-A antibody, *Anti-dsDNA* anti-dsDNA antibody, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *HIV-Ab* human immunodeficiency virus, *HPF* high power field, *WF* whole field, *NAG* N-acetyl-β-glucosaminidase, *β2MG*, β2microglobulin, *U*-protein urinary-protein

was decreased in comparison to before the treatment with prednisolone. A renal biopsy was performed two days after admission. Light microscopy revealed glomerular capillary wall thickening in periodic acid-Schiff staining and subepithelial spikes in periodic acid silver–methenamine staining (Fig. 2). Focal lymphocytic infiltration around sclerotic glomerulus and mild interstitial fibrosis were observed. Immunofluorescence microscopy showed diffuse granular capillary wall staining of IgG, IgA, and IgM and light staining of C3 (Fig. 3). In the IgG subclass analysis, IgG4 was predominant (Fig. 4), while the Phospholipase A2 receptor (PLA2R) was negative. Transmission electron microscopy showed subepithelial electron-dense deposits (Fig. 2). Taken together, the patient was diagnosed with MN. The cause of secondary MN was not found, including malignant tumors, collagen disease, or infections, nor was it drug-related. The progression of hypoproteinemia and hypercholesterolemia was observed. Considering the nephrotic syndrome and the worsening condition of CCS, the dose of prednisolone was increased to 30 mg/day. Renin–angiotensin system inhibitor was not applied because he had no history of hypertension and the blood pressure was low during hospitalization. The clinical symptoms of hair loss and nail atrophy gradually improved after the increase in the prednisolone dose, and endoscopic analysis showed an improvement in the polypoid lesions without tumor. On the other hand, the nephrotic-range proteinuria persisted even three months after the steroid dose was increased. Therefore, we added

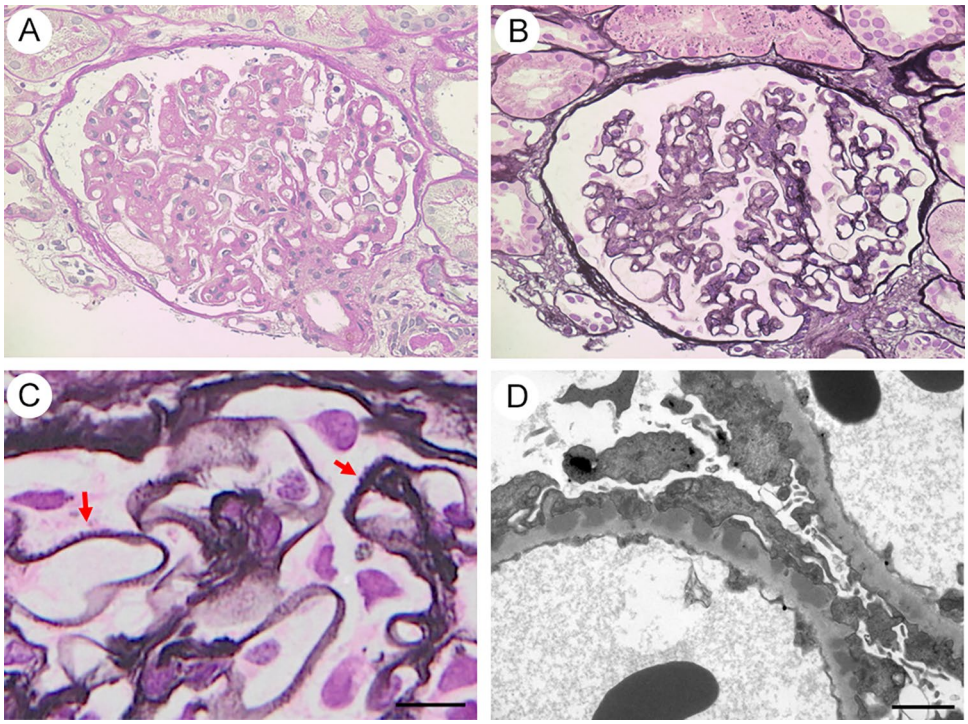

Fig. 2 Pathological findings of renal biopsy specimens. **A** Thickening of glomerular basement membrane with periodic acid-Schiff staining. **B** Subepithelial spike appearance with periodic acid-methenamine silver staining. **C** Subepithelial spike (red arrows) with periodic acid-methenamine silver staining. Scale bar: 10 µm. **D** Transmission electron microscopy images, showing subepithelial electron-dense deposits. Scale bar: 20 µm

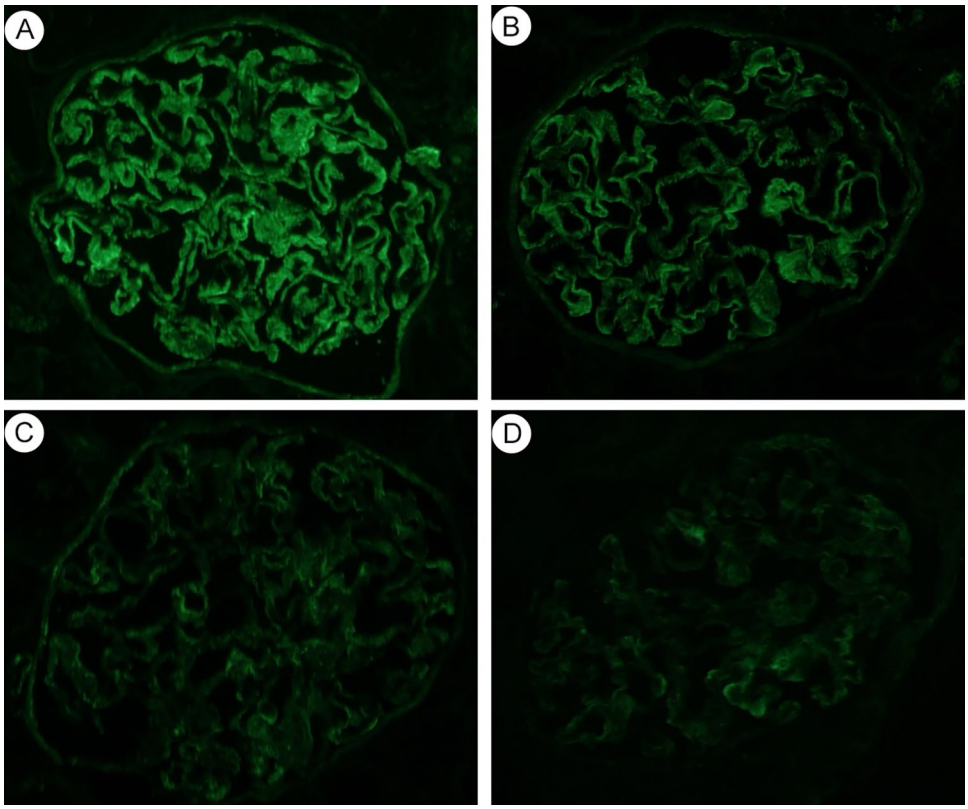

Fig. 3 Immunofluorescence findings of renal biopsy specimens. Immunofluorescence staining of IgG (**A**), IgA (**B**), C3 (**C**) and C1q (**D**), showing diffuse granular capillary wall staining of IgA and IgA, and weekly of C3

cyclosporine for the patient's steroid-resistant MN. However, severe proteinuria persisted for another five months; thus, we further added mizoribine to prednisolone and cyclosporine, which led to the decrease in proteinuria and the increase in the serum albumin concentration, which finally achieved incomplete remission type 1 (Fig. 5).

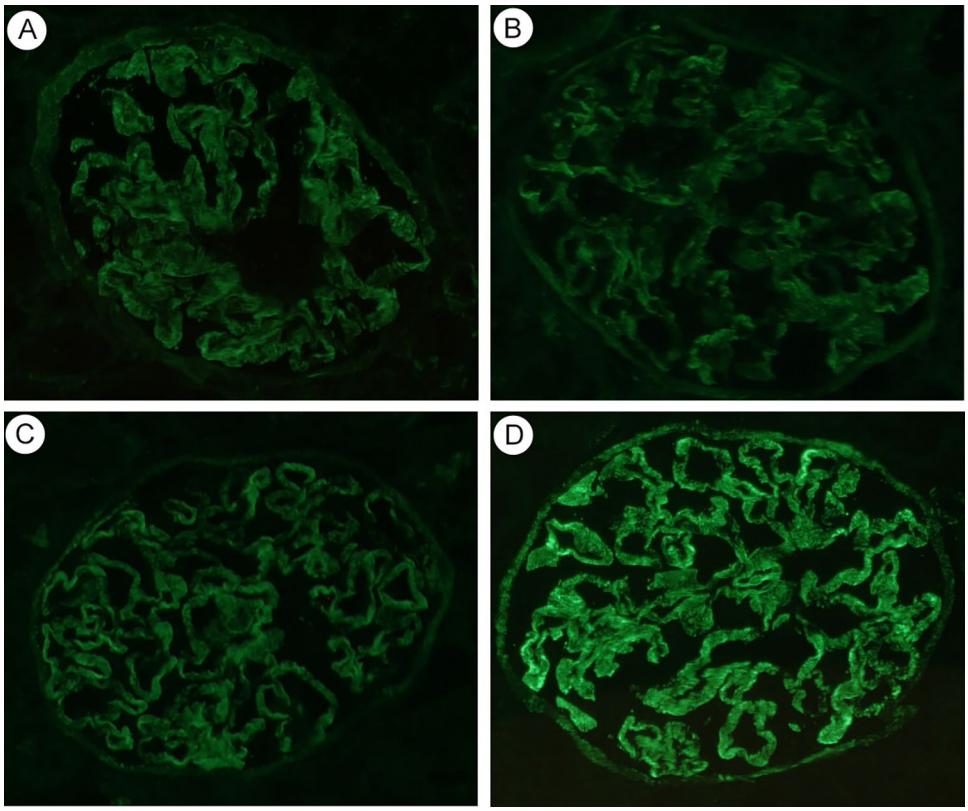

Fig. 4 Immunofluorescence findings of renal biopsy specimens for IgG subclass. Immunofluorescence staining of subclass, IgG1 (**A**), IgG2 (**B**), IgG3 (**C**) and IgG4 (**D**), showing diffuse granular capillary wall staining (IgG4 > IgG1, IgG2, IgG3)

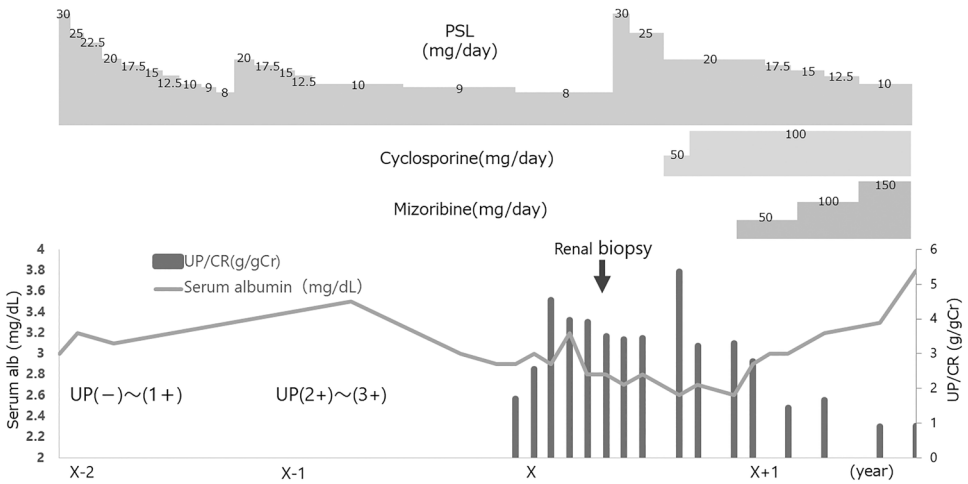

Fig. 5 Patient's clinical course. *PSL* Prednisolone, *UP* Urinary protein, *CR* Creatinine

Considering the quick response after mizoribine, we conclude that mizoribine was effective for steroid-resistant nephrotic syndrome in this case.

Discussion

CCS was first described in 1955 as a rare non-hereditary disorder manifested by diffuse gastrointestinal polyposis with associated ectodermal changes, including hair loss, hyperpigmentation, and nail atrophy [7]. Only approximately 500 CCS cases have been reported worldwide [8]. Many of the reports are from Japan. Among them, in the largest cohort of 210 patients with CCS from Japan, the average age of diagnosis was 63.5 years, and the male to female ratio of cases was 1.8 to 1 [9]. The etiology of CCS remains unclear, likely owing to the rarity of CCS. Several factors have shown to be associated with CCS, such as genetic mutations [10, 11], stress [12], low-turnover cell differentiation [13, 14], *Helicobacter pylori* infection [15, 16], and allergic reactions [17, 18]. Some studies have suggested that CCS may have an autoimmune background. For example, it was reported

that hamartomatous polyps in CCS are infiltrated with IgG4 positive plasma cells, and this finding was the first clue to the pathophysiology of CCS [1]. CCS has been reported to be associated with antinuclear antibodies [12, 17, 19, 20], and autoimmune diseases such as hypothyroidism [2, 3], systemic lupus erythematosus [4], Basedow's disease [5], and type 1 diabetes [6]. Immunosuppression using corticosteroids or long-term azathioprine may eradicate or lessen the manifestations of CCS, which is consistent with an autoimmune mechanism [21].

MN is an autoimmune disease characterized by a thickening of glomerular capillary walls, which result from immune complexes along the subepithelial region of the glomerular basement membrane. MN has been classified as idiopathic or secondary MN, based on clinical and pathological clues. Different distribution patterns of glomerular IgG subclass deposits are observed in patients with glomerular disease, and a predominant glomerular deposition of IgG4 is characteristic of idiopathic MN in general [22, 23]. In 2009, PLA2R was identified as a target antigen in idiopathic MN, and the anti-PLA2R autoantibodies were mainly IgG4 in the predominant immunoglobulin subclass in glomerular deposits [24]. Approximately 70% of patients with idiopathic MN had autoantibodies to PLA2R in their serum [24], while the prevalence of anti-PLA2R antibodies in Japanese patients was about 50%, lower than that of European and other Asian countries[25, 26]. In addition, other proteins, such as thrombospondin type 1 domain–containing 7A (THSD7A), exotosin 1 (EXT1), exotosin 2 (EXT2), neural epidermal growth factor-like 1 protein (NELL1), semaphorin 3B (Sema3B), and protocadherin 7 (PCDH7), have been shown to be etiological antigens [27], although they are less frequent. Secondary MN occurs due to malignancy, autoimmune/collagen vascular disease, infection, or drug exposure, and the treatment for the underlying disorder is expected to lead to the resolution of MN [28].

Among the patients with CCS, seven cases in combination with MN have been reported (Table 2) [3, 6, 19, 29–32], three cases of which were associated with malignancies, while others were not. MN is one of the important causes of paraneoplastic glomerulonephritis. The prevalence of gastric or colon cancer among the patients with CCS is approximately 10–20%, significantly higher than the prevalence among the general Japanese population [9, 33]; thus, it is necessary to conduct a search assuming that CCS patients with MN may have malignant tumors. In several cases, including the present case, cancer was not found by the esophagogastroduodenoscopy, colonoscopy, and capsule enteroscopy, suggesting that the development of MN in patients with CCS is not always related to malignancy [29]. Regarding the onset of CCS and MN, there are both cases in which CCS first developed and MN first developed (Table 2). In several cases, including the present case, the onset of MN was accompanied by worsening of CCS during steroid tapering; thus it is likely that the onset of MN is secondary to CCS. On the other hand, there were cases in which the onset of MN was not accompanied by worsening of CCS, though it may be due to the effects with introduced steroid or immunosuppressant.

While it is unknown whether MN and CCS are related, the combination rate with MN seems to be high, considering of the rarity of CCS. In addition, no other cases of the combination with nephritis, except for MN, have been reported so far, suggesting a possible association between CCS and MN. Importantly, we first indicated that IgG4 was predominantly stained in renal biopsy specimens of CCS patients, using immunofluorescent analysis. It was reported that CCS hamartomatous polyps are infiltrated with IgG4 plasma cells [1]; thus, CCS and its associated MN may have a common autoimmune mechanism related to IgG4. Nevertheless, in our present case, immunohistochemical analysis of IgG4 of small intestine was negative. Further exploration of association between MN and CCS is required.

Current CCS treatment mainly uses steroids, and other reported treatments include 5-aminosalicylate acid, histamine H2 receptor antagonists, anti-tumor necrosis factor α agents, and immunomodulators [9]. 80–91% of patients with CCS respond to corticosteroids; however, relapse is commonly observed under steroid tapering, and it was reported that azathioprine or cyclosporine may be a therapeutic option for the treatment of CCS [9, 21, 34]. The treatment for MN in patients with CCS has not been established. According to the previous literature, treatment for MN in patients with CCS included prednisolone [19], cyclosporine [29]. In one case, cyclosporine was not effective for patients with steroid-resistant MN, and rituximab was effective [3]. Rituximab is an anti-CD20 chimeric antibody that depletes B cells via complement-mediated and antibody-dependent cell cytotoxicity [35]; thus, the effectiveness of rituximab supports the hypothesis that the mechanism of MN in patients with CCS is associated with B cells. In the present case, proteinuria decreased by adding mizoribine to prednisolone and cyclosporine. Mizoribine is an imidazole nucleoside and an immunosuppressive agent, which inhibits DNA synthesis in the S phase of the cell cycle and both humoral and cellular immunity by selectively inhibiting lymphocyte proliferation [36]. Furthermore, mizoribine suppresses antibody production and proliferation of B cells by acting directly on B cells [37]. Therefore, the effect of mizoribine on B cells may be effective for MN in patients with CCS. Although further prospective studies are needed to confirm its effectiveness, our case suggests that mizoribine may be an option for patients with steroid-resistant MN.

CCS patients have chronic diarrhea and protein-losing enteropathy at a high rate, and the mean serum albumin level is reported to be low (2.96 ± 0.74 g/dL at the time of

Table 2 Reported cases of CCS Associated with MN

Ref	Age/Sex	Malignancy complications	Onset of MN/CCS	s-Alb (g/dL)	Urine protein	Treatment for CCS	Treatment for MN	Renal outcome	Renal biopsy			Gastric/colon polyp biopsy
									IF	IgG4/PLA2R	EM	IgG4
This case	57/M	No malignancy pituitary adenoma atopic dermatitis	CCS → MN after PSL↓	3.2	3.9 g/gCr	PSL	CyA + MZB	CyA: ineffective MZB:incomplete remission	IgG/IgA/IgM/C3	Positive/Negative	Stage II	Negative
[29]	47/M	No malignancy GOO	CCS → MN after PSL↓	3.0	14.3 g/gCr	PSL	PSL + CyA	Remission	IgG/IgA	–	–	–
[3]	71/M	No malignancy hypothyroidism	CCS → MN after PSL↓	–	4.4 g/day	PSL + AZA	CyA + RTX	CyA: ineffective RTX: remission	IgG/C3	–	–	Positive
[30]	57/M	No malignancy	CCS → MN after PSL↓	3.0	1.43 g/day	PSL	None	Remission	IgG/C3	–	Stage I	Negative
[31]	59/M	Gastric cancer	MN → CCS 30 years after MN	1.8	–	Operation	–	Unknown	–	–	–	–
[19]	64/M	Colon cancer high titer of ANA	CCS → MN after cancer surgery / PSL discontinuation	3.0	3.5–4.2 g/day	None	PSL	Remission	IgG/C3	–	–	–
[32]	41/M	Rectal cancer hepatitis B PLE	MN → CCS 5 years after MN	2.6	–	Operation	None	Ineffective	–	–	–	–
[6]	17/M	No malignancy type 1 diabetes thalassemia	CCS → MN	1.9	7.9–9.6 g/day	None	CyA	Remission (relapse after discontinuation)	–	–	Stage III	–

Ref reference, *EM* electron microscope, *IF* immunofluorescence staining, *CyA* cyclosporine, *MZB* mizoribine, *PSL* prednisolone, *AZA* azathioprine, *GOO* gastric outlet obstruction, *RTX* rituximab, *PLE* protein-losing enteropathy

diagnosis) [9]. Indeed, more than 88% of CCS patients were reported to develop hypoalbuminemia [38]. Therefore, it is possible to overlook proteinuria without a urinalysis, even if CCS patients exhibit hypoalbuminemia due to nephritic syndrome.

In conclusion, there may be an association between MN and CCS. Mizoribine may be an effective option for CCS patients with steroid-resistant MN. Proteinuria might be overlooked, considering the hypoproteinemia due to chronic diarrhea and protein-losing enteropathy that frequently complicate CCS. Therefore, we would like to highlight the importance of follow-up urinalysis in patients with CCS for the early detection of MN, which may occur concurrently.

Declarations

Conflict of interest The authors declare that they have no competing interest.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from participants included in the article.

References

1. Riegert-Johnson DL, Osborn N, Smyrk T, Boardman LA. Cronkhite–Canada syndrome hamartomatous polyps are infiltrated with IgG4 plasma cells. Digestion. 2007;75(2–3):96–7. https://doi.org/10.1159/000102963.
2. Qiao M, Lei Z, Nai-Zhong H, Jian-Ming X. Cronkhite–Canada syndrome with hypothyroidism. South Med J. 2005;98(5):575–6. https://doi.org/10.1097/01.SMJ.0000157528.71614.C4.
3. Firth C, Harris LA, Smith ML, Thomas LF. A case report of Cronkhite–Canada syndrome complicated by membranous nephropathy. Case Rep Nephrol Dial. 2018;8(3):261–7. https://doi.org/10.1159/000494714.
4. Kubo T, Hirose S, Aoki S, Kaji T, Kitagawa M. Canada-Cronkhite syndrome associated with systemic lupus erythematosus. Arch Intern Med. 1986;146(5):995–6.
5. Ota S, Kasahara A, Tada S, Tanaka T, Umena S, Fukatsu H, et al. Cronkhite–Canada syndrome showing elevated levels of antinuclear and anticentromere antibody. Clin J Gastroenterol. 2015;8(1):29–34. https://doi.org/10.1007/s12328-014-0547-6.
6. Vernia P, Marcheggiano A, Marinaro V, Morabito S, Guzzo I, Pierucci A. Is Cronkhite–Canada syndrome necessarily a late-onset disease? Eur J Gastroenterol Hepatol. 2005;17(10):1139–41. https://doi.org/10.1097/00042737-200510000-00022.
7. Cronkhite LW Jr, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Engl J Med. 1955;252(24):1011–5. https://doi.org/10.1056/NEJM195506162522401.
8. Hu H, Wu Y, Zhang Y, Zhang L, Zhang J, Zhang R. Comprehensive treatment of Cronkhite–Canada syndrome: a case report and literature review. Medicine (Baltimore). 2023;102(6): e32714. https://doi.org/10.1097/MD.0000000000032714.
9. Watanabe C, Komoto S, Tomita K, Hokari R, Tanaka M, Hirata I, et al. Endoscopic and clinical evaluation of treatment and prognosis of Cronkhite–Canada syndrome: a Japanese nationwide survey. J Gastroenterol. 2016;51(4):327–36. https://doi.org/10.1007/s00535-015-1107-7.
10. Patil V, Patil LS, Jakareddy R, Verma A, Gupta AB. Cronkhite–Canada syndrome: a report of two familial cases. Indian J Gastroenterol. 2013;32(2):119–22. https://doi.org/10.1007/s12664-012-0296-8.
11. 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(5):746–8. https://doi.org/10.1038/ajg.2016.92.
12. Murata I, Yoshikawa I, Endo M, Tai M, Toyoda C, Abe S, et al. Cronkhite–Canada syndrome: report of two cases. J Gastroenterol. 2000;35(9):706–11. https://doi.org/10.1007/s005350070051.
13. Freeman K, Anthony PP, Miller DS, Warin AP. Cronkhite–Canada syndrome: a new hypothesis. Gut. 1985;26(5):531–6. https://doi.org/10.1136/gut.26.5.531.
14. 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(2):145–8. https://doi.org/10.1111/ajd.12068.
15. Okamoto K, Isomoto H, Shikuwa S, Nishiyama H, Ito M, Kohno S. A case of Cronkhite–Canada syndrome: remission after treatment with anti-*Helicobacter pylori* regimen. Digestion. 2008;78(2–3):82–7. https://doi.org/10.1159/000165354.
16. 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(1):140–6. https://doi.org/10.1159/000350321.
17. Wen XH, Wang L, Wang YX, Qian JM. Cronkhite–Canada syndrome: report of six cases and review of literature. World J Gastroenterol. 2014;20(23):7518–22. https://doi.org/10.3748/wjg.v20.i23.7518.
18. Wu ZY, Sang LX, Chang B. Cronkhite–Canada syndrome: from clinical features to treatment. Gastroenterol Rep (Oxf). 2020;8(5):333–42. https://doi.org/10.1093/gastro/goaa058.
19. Takeuchi Y, Yoshikawa M, Tsukamoto N, Shiroi A, Hoshida Y, Enomoto Y, et al. Cronkhite–Canada syndrome with colon cancer, portal thrombosis, high titer of antinuclear antibodies, and membranous glomerulonephritis. J Gastroenterol. 2003;38(8):791–5. https://doi.org/10.1007/s00535-002-1148-6.
20. Sampson JE, Harmon ML, Cushman M, Krawitt EL. Corticosteroid-responsive Cronkhite–Canada syndrome complicated by thrombosis. Dig Dis Sci. 2007;52(4):1137–40. https://doi.org/10.1007/s10620-006-9375-y.
21. 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(2):496–502. https://doi.org/10.1007/s10620-011-1874-9.
22. Doi T, Mayumi M, Kanatsu K, Suehiro F, Hamashima Y. Distribution of IgG subclasses in membranous nephropathy. Clin Exp Immunol. 1984;58(1):57–62.
23. Ohtani H, Wakui H, Komatsuda A, Okuyama S, Masai R, Maki N, et al. Distribution of glomerular IgG subclass deposits in malignancy-associated membranous nephropathy. Nephrol Dial Transplant. 2004;19(3):574–9. https://doi.org/10.1093/ndt/gfg616.
24. Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):11–21. https://doi.org/10.1056/NEJMoa0810457.
25. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, Seitz-Polski B, Ma H, Zahner G, et al. Thrombospondin type-1 domain-containing

7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371(24):2277–87. https://doi.org/10.1056/NEJMoa1409354.
26. Iwakura T, Ohashi N, Kato A, Baba S, Yasuda H. Prevalence of enhanced granular expression of thrombospondin type-1 domain containing 7A in the glomeruli of Japanese patients with idiopathic membranous nephropathy. PLoS ONE. 2015;10(9): e0138841. https://doi.org/10.1371/journal.pone.0138841.
27. Sethi S. New 'antigens' in membranous nephropathy. J Am Soc Nephrol. 2021;32(2):268–78. https://doi.org/10.1681/ASN.2020071082.
28. Alsharhan L, Beck LH Jr. Membranous nephropathy: core curriculum 2021. Am J Kidney Dis. 2021;77(3):440–53. https://doi.org/10.1053/j.ajkd.2020.10.009.
29. Onozato Y, Sasaki Y, Abe Y, Yaoita T, Yagi M, Mizumoto N, et al. Cronkhite–Canada syndrome associated with gastric outlet obstruction and membranous nephropathy: a case report and review of the literature. Intern Med. 2020;59(22):2871–7. https://doi.org/10.2169/internalmedicine.5278-20.
30. Watanabe T, Otsuki Y, Suzuki Y. Cronkhite–Canada syndrome ni taisuru suteroidotiryoutsuu ni makuseizinshou wo hassyou sita itirei (in Japanese). Jpn J Hosp Gen Med. 2018;14(6):581–3.
31. Karasawa H, Miura K, Ishida K, Sase T, Kobayashi T, Kinouchi M, et al. Cronkhite–Canada syndrome complicated with huge intramucosal gastric cancer. Gastric Cancer. 2009;12(2):113–7. https://doi.org/10.1007/s10120-009-0506-y.
32. Yamaguchi K, Ogata Y, Akagi Y, Sasatomi T, Ozaki K, Ohkita A, et al. Cronkhite–Canada syndrome associated with advanced rectal cancer treated by a subtotal colectomy: report of a case. Surg Today. 2001;31(6):521–6. https://doi.org/10.1007/s005950170114.
33. Isobe T, Kobayashi T, Hashimoto K, Kizaki J, Miyagi M, Aoyagi K, et al. Cronkhite–Canada syndrome complicated with multiple gastric cancers and multiple colon adenomas. Am J Case Rep. 2013;14:120–8. https://doi.org/10.12659/AJCR.889083.
34. Yamakawa K, Yoshino T, Watanabe K, Kawano K, Kurita A, Matsuzaki N, et al. Effectiveness of cyclosporine as a treatment for steroid-resistant Cronkhite–Canada syndrome; two case reports. BMC Gastroenterol. 2016;16(1):123. https://doi.org/10.1186/s12876-016-0541-1.
35. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene. 2003;22(47):7359–68. https://doi.org/10.1038/sj.onc.1206939.
36. Kawasaki Y. Mizoribine: a new approach in the treatment of renal disease. Clin Dev Immunol. 2009. https://doi.org/10.1155/2009/681482.
37. Kamada H, Itoh H, Shibata H, et al. Inhibitory mechanism of mizoribine on the antibody production of mouse B cells stimulated with lipopolysaccharide. Jpn J Pharmacol. 1997;74(4):323–30. https://doi.org/10.1254/jjp.74.323.
38. Liu Y, Zhang L, Yang Y, et al. Cronkhite–Canada syndrome: report of a rare case and review of the literature. J Int Med Res. 2020;48(5):300060520922427. https://doi.org/10.1177/0300060520922427.