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CASE REPORT

Association between Crohn's disease and AarF domain-containing kinase 4 glomerulopathy

Toshihiko Kakiuchi[1] · Yasufumi Ohtsuka[1] · Tadashi Sato[2] · Aiko Nakayama[1] · Kumiko Jinnouchi[1] · Masafumi Oka[2] · Muneaki Matsuo[1]

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Abstract
Coenzyme Q10 deficiency causing gastrointestinal symptoms has not been reported. At least 15 genes are involved in CoQ10 biosynthesis, and one of the genes is AarF domain-containing kinase 4 (*ADCK4*). This case report first showed a patient who presented with Crohn's disease (CD) combined with *ADCK4* glomerulopathy (ADCK4-GN). After approximately 2 years of infliximab treatment for CD, this patient has remained in clinical remission with no adverse effects. Moreover, two important findings were obtained: first, individuals with ADCK4-GN may present with complications, such as CD, which is a gastrointestinal disease, and infliximab may be effective for CD associated with ADCK4-GN. Second, infliximab may also be effective and safe for individuals with CD who are undergoing peritoneal dialysis. Thus, the results of the present study may be used in managing patients with such condition, and as a result, better clinical outcomes will be obtained.

Keywords AarF domain-containing kinase 4 glomerulopathy · Crohn's disease · Infliximab · Peritoneal dialysis

Introduction

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a fat-soluble component consisting of a quinone skeleton and ten isoprenoids. It is essential in electron transfer systems. At least 15 genes are involved in CoQ10 biosynthesis [1, 2], and one of the genes is AarF domain-containing kinase 4 (*ADCK4*), which is located on human chromosome 19q13.2 and encodes the ADCK4 protein, which interacts with the members of the CoQ10 biosynthesis pathway. Mutations in *ADCK4* can cause CoQ10 deficiency and mitochondrial nephropathy [ADCK4-associated glomerulopathy, (ADCK4-GN)] [3, 4]. To date, whether CoQ10 deficiency can cause gastrointestinal symptoms has not been reported. Here, we report the first case of Crohn's disease (CD) combined with ADCK4-GN.

✉ Toshihiko Kakiuchi
kakiucht@cc.saga-u.ac.jp

[1] Department of Pediatrics, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga-shi, Saga 849-8501, Japan

[2] Department of Pediatrics, Ureshino Medical Center, 2436, Shimojuku-hei, Oaza, Ureshino-machi, Ureshino-shi, Saga 843-0393, Japan

Case report

A 16-year-old boy presented with ADCK4-GN and end-stage renal failure. At the age of 6 years, he presented with proteinuria according to the results of his urinalysis conducted at school. He underwent renal biopsy at the age of 10 years and was later diagnosed with minimal change disease with nodular glomerulosclerosis.

Moreover, his younger brother who was 4 years younger than him also presented with proteinuria during his medical checkup at the age of 3 years. Renal biopsy was performed at the age of 9 years, and he was diagnosed with focal glomerulosclerosis. At the age of 10 years, he presented with end-stage renal failure. At this time, hereditary kidney disease was suspected. Using his brother's peripheral blood DNA, exosome analysis was performed with next-generation sequencing. In total, 92 genes involved in nephrotic syndrome, focal glomerulosclerosis, and renal failure were identified, and 583 mutations were observed, of which one mutation related to *ADCK4* was found using homozygous 306 variants. Using Sanger sequencing, the 737 G>A heterozygous mutation was found in the parents, and the patient and his brother also presented with the same mutation as a homozygote. Based on these results, they were diagnosed with ADCK4-GN. The serum concentration of CoQ10 was

1268 nmol/L (normal range 389–1215 nmol/L). After the diagnosis was confirmed, CoQ10 1200 mg PO, once daily was started.

At 16 years and 5 months, the patient presented with fever, diarrhea, perianal abscess, and weight loss. Incisional drainage was performed for perianal abscess. However, the condition was not improved. Thus, the patient was referred to the division of pediatric gastroenterology. His laboratory data were as follows: increased C-reactive protein level, 1.49 (normal range < 0.19) mg/dL; increased erythrocyte sedimentation rate, 84 mm/h; increased serum amyloid A protein level, 131 (normal range < 8.0) μg/dL; increased blood urea nitrogen level, 51.1 mg/dL; increased serum creatinine level, 3.45 mg/dL; hypoalbuminemia, 3.3 g/dL; hypocholesterolemia, 107 mg/dL; and moderate anemia, hemoglobin level 10.8 g/dL (Table 1). Barium enema study revealed multiple small niche reflecting aphtha in continuity to the distal ileum, which was approximately 30–40 cm (Fig. 1a). Magnetic resonance imaging showed no perianal abscess or anal fistula. However, the patient's intestinal wall thickened, similar to an edema (Fig. 1b). On total colonoscopy, multiple aphtha was observed in the ileum approximately 10 cm from the ileocecal area. However, no longitudinal ulcer was observed (Fig. 1c, d). No abnormal finding was observed in the total colon. Histopathological findings at the site of aphtha included the infiltration of lymphocytes, plasma cells, and neutrophils into the mucosal lamina propria interstitium. Moreover, lymphoid follicular-like structure and epithelioid granuloma were noted (Fig. 2a–c). On esophagogastroduodenoscopy, no abnormal findings were observed. Negative results were obtained in the following tests: hepatitis C virus antibody, hepatitis B surface antigen, hepatitis B core antibody, cytomegalovirus antigenemia, stool culture, fecal smear inspection, fecal microbial ova-parasite examination, interferon-gamma release assays, tuberculin skin test, and *Clostridium difficile* toxin test. Therefore, the patient was diagnosed with CD according to Porto criteria [5], and his Pediatric Crohn's Disease Activity Index (PCADI) was 27.5 points. Figure 3 showed the clinical course. Treatment with 5-aminosalicylic acid (750 mg/day) and half-dose elemental diet therapy were initiated. However, the patient's clinical findings and blood test results worsened, and no improvement was observed. Thus, the use of infliximab was discussed with the patient; 5 mg/kg of infliximab was administered at 0, 2 and 6 weeks and every 8 weeks thereafter. After the initiation of infliximab, a substantial improvement was observed, as evidenced by both clinical and laboratory parameters; no further impairment in renal function was observed. The PCADI score decreased to < 10 points. Peritoneal dialysis was initiated, scheduled after the third infliximab administration. After approximately 2 years of infliximab treatment, the patient has remained in clinical remission with no adverse effects.

Discussion

The patient's disease course provided two important clinical suggestions. First, individuals with ADCK4-GN may present with complications, such as CD, which is a gastrointestinal disease, and that infliximab may be effective for CD associated with ADCK4-GN. Mutations in *ADCK4* cause mitochondrial dysfunction, resulting in the development of neurological, muscle, and kidney diseases [1]. However, to date, the development of gastrointestinal disease has not been assessed. In animal experiments, the anti-inflammatory effect of CoQ10 on ulcerative colitis has been reported [6]; therefore, CoQ10 deficiency due to *ADCK4* gene mutation may cause inflammation in the intestinal tract to human beings. In this case, *ADCK4* gene mutation has been proved, but the serum CoQ10 concentration was slightly higher than the normal value. However, it has been reported that CoQ10 concentration does not correlate with serum and organ tissues [7], and that it is difficult to increase CoQ10 concentration in organ tissues even when administered exogenously [8]. In this case, the concentration of CoQ10 other than serum could not be measured, but due to the *ADCK4* abnormality it was considered possible that the CoQ10 concentration in the gastrointestinal tract decreased to cause mitochondrial

Table 1 Blood test and biochemical test results at the onset of enteritis

WBC	11,800	/μL	Alb	3.3	g/dL
Hb	10.8	g/dL	AST	131	IU/L
Plt	49.4×10^4	/μL	ALT	71	IU/L
			LDH	154	IU/L
ESR	84	mm/1 h	CK	48	IU/L
			CRP	1.49	mg/dL
BUN	51.1	mg/dL	SAA	131	μg/dL
Cr	3.45	mg/dL			
eGFR	24.8	mL/min/1.73 m^2			
K	4.6	mmol/L			

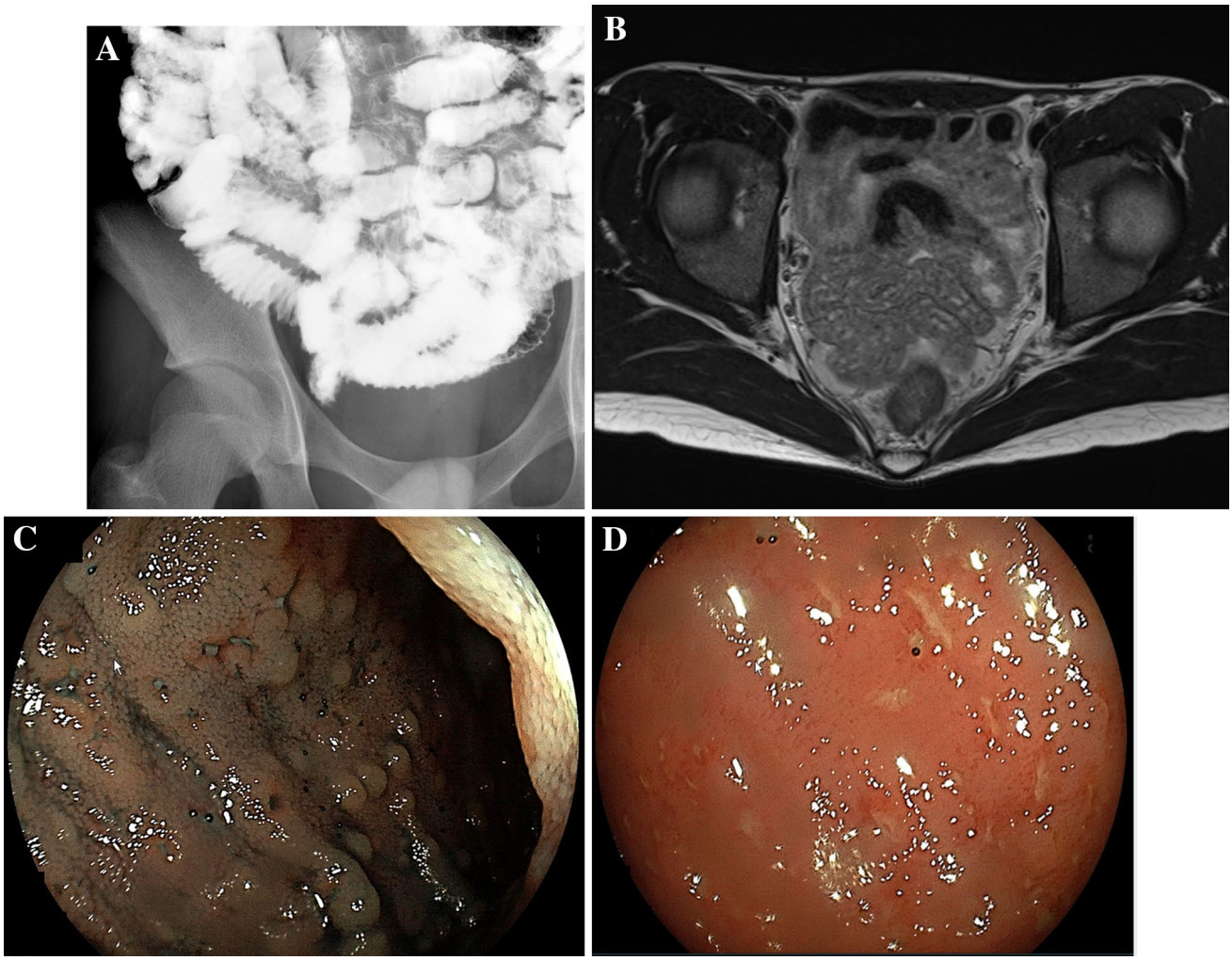

Fig. 1 **a** Barium enema findings included multiple small niche reflecting aphtha in the ileum approximately 10 cm from the ileocecal area. **b** Magnetic resonance imaging showed intestinal wall thickened, similar to an edema. **c, d** Total colonoscopy findings included small multiple aphtha in the ileum

dysfunction and cause CD. Infliximab has been shown to be effective in mitochondrial respiratory chain complex disorders [9]; similar efficacy was observed in our case. Thus, infliximab could be effective for CD associated with mitochondrial dysfunction disorders.

Second, infliximab may also be effective and safe for individuals with CD who are undergoing peritoneal dialysis. Furthermore, this drug is effective in individuals with CD who are undergoing hemodialysis [10]. However, there has been no study on the use of infliximab in patients with CD who are undergoing peritoneal dialysis. Moreover, concentrations of infliximab in the blood do not decrease before and after hemodialysis [11]. Thus, infliximab could be effective even in individuals undergoing peritoneal dialysis. As peritoneal dialysis improves the quality of life, our case may be used as a basis when choosing the dialysis method for patients with CD requiring infliximab.

In conclusion, individuals with ADCK4-GN may present with complications, such as CD. Infliximab is effective for CD associated with ADCK4-GN and may also be effective and safe for individuals with CD who are undergoing peritoneal dialysis.

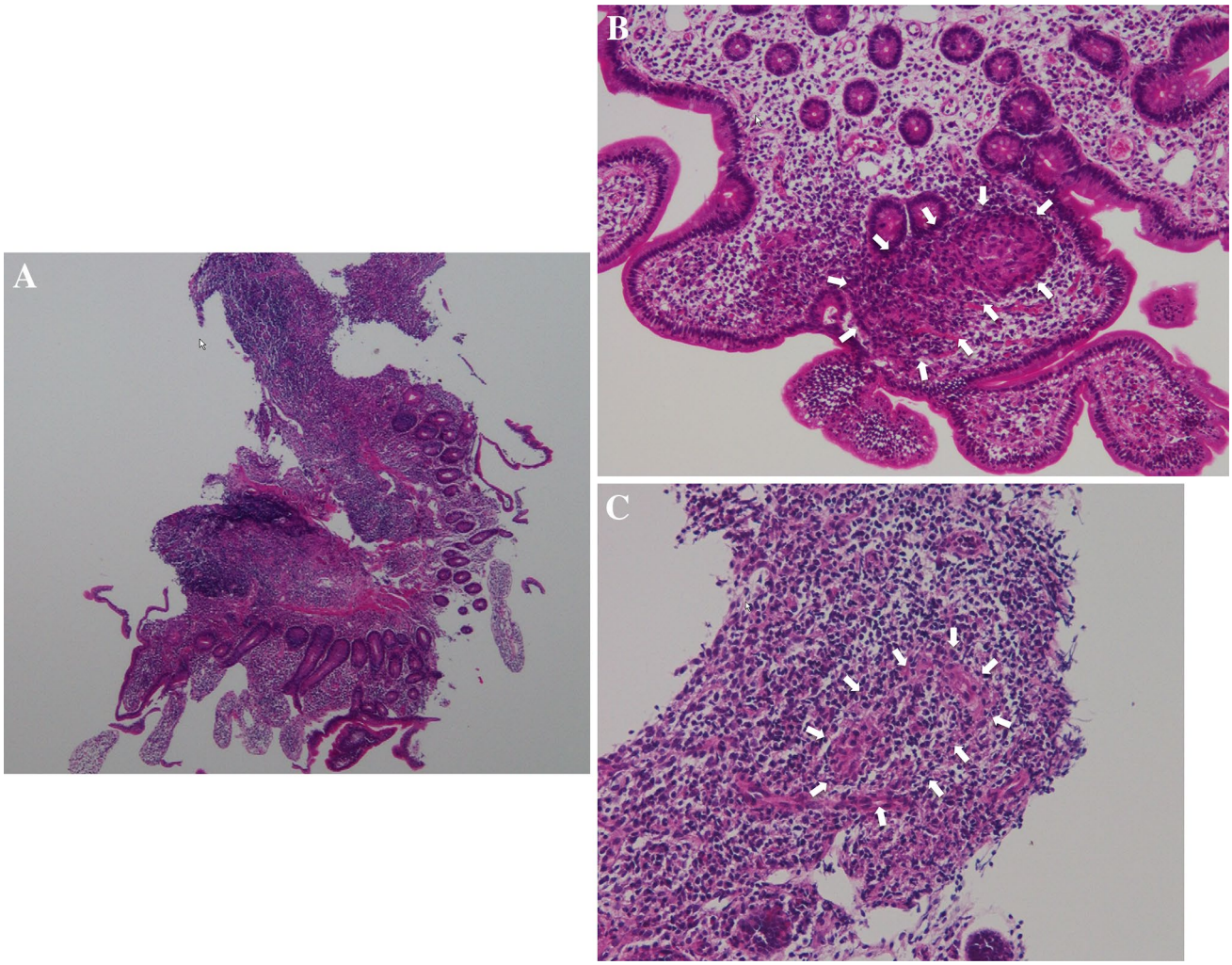

Fig. 2 **a** Histopathological findings included the infiltration of lymphocytes, plasma cells, and neutrophils into the mucosal lamina propria interstitium (HE stain 40×) and **b, c** the presence of lymphoid follicular-like structure and epithelioid granuloma (HE stain 200×). The areas surrounded by the dotted line were epithelioid granuloma. *HE* hematoxylin and eosin

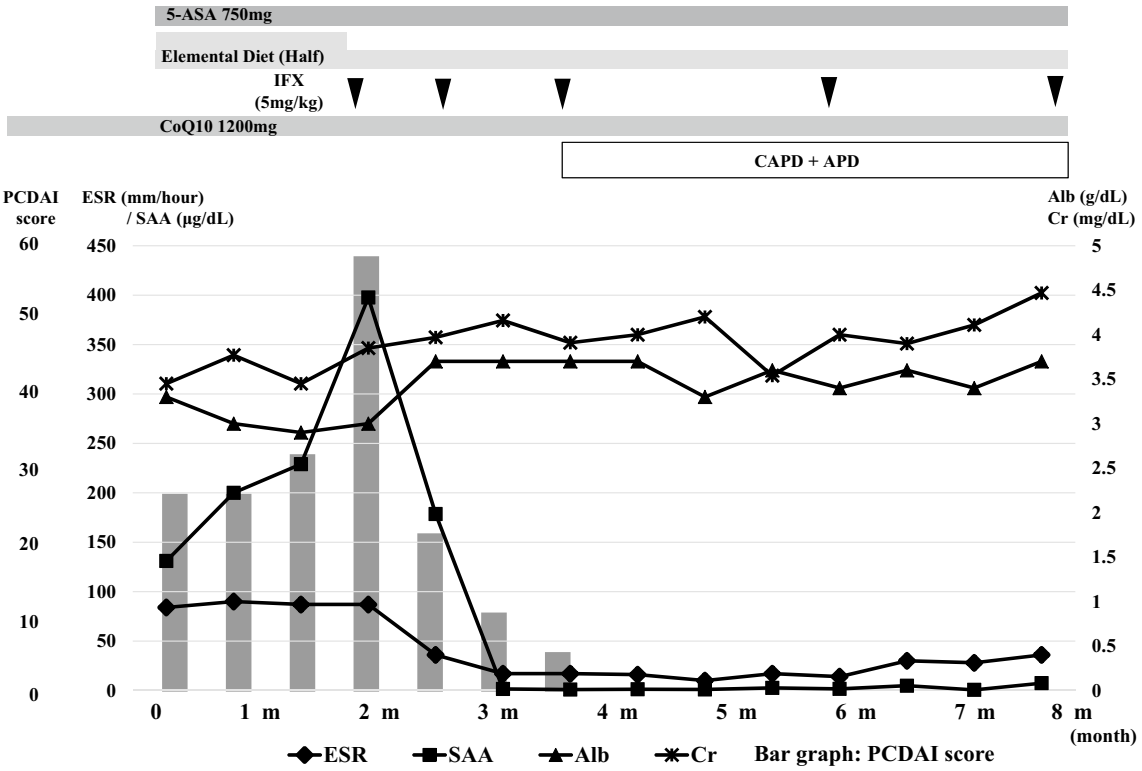

Fig. 3 Clinical course of the patient. Infliximab was administered at a dose of 5 mg/kg at 0, 2, and 6 weeks and every 8 weeks thereafter. After the initiation of infliximab, a substantial improvement was observed, as evidenced by both clinical and laboratory parameters. *5-ASA* 5-aminosalicylic acid, *IFX* infliximab, *CoQ10* coenzyme Q10, *CAPD* continuous ambulatory peritoneal dialysis, *APD* automated peritoneal dialysis, *PCDAI* Pediatric Crohn's Disease Activity Index, *ESR* erythrocyte sedimentation rate, *SAA* serum amyloid A protein, *Alb* albumin

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Author contributions As the lead author, TK was involved with all stage of patient management and wrote the manuscript. YO, TS, AN, KJ and MO performed the treatment. MM collaborated as the reviewer. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Kakiuchi T, Ohtsuka Y, Sato T, Nakayama A, Jinnouchi K, Oka M and Matsuo M declare that they no conflict of interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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