Case Report

Ulcerative Colitis Associated with Cardiometabolic Disease and Complicated with Autoimmune Pancreatitis

Mitsuro Chiba[1],*, Takeshi Miura[2], Hisanori Matsuzawa[1], Tsuyotoshi Tsuji[1], Haruhiko Tozawa[3], Akira Zeniya[4]

[1]Division of Gastroenterology, Akita City Hospital, Akita, Japan,
[2]Division of Diabetes and Metabolism, Akita City Hospital, Akita, Japan,
[3]Division of Gastroenterology, Nakadori General Hospital, Akita, Japan,
[4]Zeniya Clinic, Akita City, Japan

Diet-related cardiometabolic diseases and inflammatory bowel disease, common previously in Western countries, are global problems. We hypothesized that inflammatory bowel disease is a lifestyle disease primarily mediated by the current Western diet. We report here the simultaneous onset of ulcerative colitis and autoimmune pancreatitis, a rare systemic complication of inflammatory bowel disease, 2 months after acute myocardial infarction in a patient with type 2 diabetes. A 67-year-old man with type 2 diabetes was referred to us because of newly diagnosed ulcerative colitis 2 months after acute myocardial infarction. A plant-based diet was provided during hospitalization. An abrupt deterioration in plasma glucose and hemoglobin A1c due to asymptomatic type 2 autoimmune pancreatitis was observed. Prednisolone administration under intensive insulin therapy led to the remission of both diseases. This case was an illustrative one of association between cardiometabolic diseases and inflammatory bowel diseases caused by current unhealthy diets and their shared pathogenesis.

Keywords: Autoimmune pancreatitis, Myocardial infarction, Plantbased diet, Type 2 diabetes mellitus, Ulcerative colitis

INTRODUCTION

The incidence of diet-related obesity and cardiometabolic disease (CMD), represented by type 2 diabetes mellitus (T2D), coronary heart disease, metabolic syndrome, stroke, and metabolic-associated fatty liver disease redefined for non-alcoholic fatty liver disease (NAFLD), has been steadily increasing and is a global health concern [1]. This increase is believed to be due to dietary transition worldwide from traditional diets to westernized diets. Namely, CMD is a lifestyle disease. Current global consumption consists of an excess of unhealthy foods such as red meat, fat, sugar, and refined grains and a shortage of healthy foods such as vegetables, fruits, legumes, whole grains, and nuts [1].

Inflammatory bowel disease (IBD), a collective term for ulcerative colitis (UC) and Crohn's disease (CD), is thought to occur in a susceptible person triggered by an environmental factor in wealthy societies. However, a widely appreciated ubiquitous environmental factor for IBD is lacking, which is the biggest obstacle to providing adequate therapy in IBD. IBD has been common in wealthy nations since the latter half of the 20th century, and it has increased since the turn of the 21st century in newly industrialized countries, thereby making IBD a global disease [2]. IBD also increased with dietary transition [3]. Based on multidisciplinary evidence, we assert that IBD is a lifestyle disease mainly mediated by current westernized diets [3]. Even current well-balanced diets are unsatisfactory in both the induction and quiescent phases for IBD, particularly in CD [3]. Therefore, we replaced current diets with a plant-based diet (PBD) (lacto-ovo-vegetarian diet) during hospitalization. This modality surpassed current standards in therapeutic outcomes in both UC and CD in both the induction and quiescent phases. Consequently, we now recommend PBD for IBD [3].

Because current diets are critically responsible for CMD and IBD, these diseases are anticipated to be associated. Indeed, the association of CMD and IBD has recently been reported and appreciated [4,5].

Autoimmune pancreatitis (AIP) was first described in 1995 and it is a rare systemic complication of IBD. The international consensus diagnostic criteria for AIP were published in 2011. There are two known types of AIP with different characteristics: type 1 and type 2. The histopathology is lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric pancreatitis, respectively. Elevation of serum IgG4 is present in type 1 and absent in type 2. Both types are responsive to corticosteroid therapy. Association of IBD with AIP is observed mostly in type 2 (89/91 cases, 98%) [6]. About two-thirds of the association was reported in UC and one-third in CD [6]. Altogether, a few hundred IBD cases with AIP have been reported worldwide [6].

We encountered a case of simultaneous onset of UC and type 2 AIP in a patient with T2D. In this case, onset was 2 months after acute myocardial infarction (AMI).

CASE REPORT

A 67-year-old man was referred to us for treatment of UC (E3 extensive colitis) in the middle of March 2022. He had been taking anti-hypertensive drugs for nearly 30 years, the antiplatelet clopidogrel for lacunar stroke for nearly 15 years, and alogliptin 25 mg/metformin 500 mg combination tablet and glimepiride (2 mg) for T2D for more than 3 years. He had been a heavy smoker (219 ≥ 10 pack-years) for about 40 years. Two months previously, he suffered AMI, underwent a percutaneous coronary intervention, and a stent was implanted. Thereafter, he had been taking dual antiplatelets (aspirin and clopidogrel) and stopped smoking. There was no family history of IBD.

He had bloody diarrhea four times a day in late February 2022. Colonoscopy in early March performed by a local endoscopist revealed disappearance of vascular patterns and coarse mucosa in the entire colon, and mucopurulent exudate in the rectum. Biopsy specimens showed crypt abscesses and goblet cell depletion, which were consistent with findings of UC. Neither abdominal pain nor fever was present. His appetite was not disturbed. Therefore, educational hospitalization to experience a PBD for 2 weeks was thought to be adequate for both UC and T2D [3]. He accepted our recommendation and was hospitalized in late March. His height was 168 cm and body weight was 69 kg. Physical examination was non-contributory. Laboratory examination findings are shown in Table 1. The following blood tests were normal: differential count of white blood cells, bilirubin, liver function tests, electrolytes, and three immunoglobulins (IgG, IgA, and IgM). The severity of UC was moderate. PBD (lacto-ovo-vegetarian diet) 1,700 kcal/day was provided [3]. Soon after admission, deteriorated plasma glucose and hemoglobin A1c (HbA1c) levels compared to those 10 days previously were unexpectedly found: from 258 to 449 mg/dL and 7.3 to 8.0%, respectively (Table 1, Fig. 1). Proteinuria was absent, but increased microalbuminuria (50.7 mg/day) was found (reference < 30). There were no signs of diabetic retinopathy. At this point, we told him that the duration of hospitalization would be extended. Insulin therapy, lispro (4-4-4-0 units) and glargine (0-0-0-4 units), was initiated (Fig. 1). Laboratory data ruled out type 1 diabetes mellitus due to an absence of anti-glutamic acid decarboxylase antibody (Table 1). Both amylase and lipase were elevated (Table 1, Fig. 1). Morphological studies with computed tomography (CT) and magnetic resonance cholangio-pancreatography revealed swelling of the pancreas with rim and slight narrowing of the main pancreatic duct, indi-

Table 1. Laboratory findings

Item	Reference	-5 HD	6 HD	36 HD	18 months F/U
White blood cell	3,300-8,600/μL	6,000	5,600	10,100[a]	8,600
Hemoglobin	13.7-16.8 g/dL	14.1	13.2[a]	14.5	15.1
Platelet	$15.8\text{-}34.8 \times 10^4/\mu L$	33.2	30.4	21.6	25.7
Total cholesterol	128-219 mg/dL	142	122	153	143
LDL-cholesterol	60-139 mg/dL	102	n.t.	n.t.	64
Triglyceride	30-149 mg/dL	102	n.t.	82	159[a]
Uria nitrogen	8-20 mg/dL	15.5	17.8	20.2[a]	20.9[a]
Creatinine	0.65-1.07 mg/dL	0.91	1.06	1.03	0.97
Total protein	6.6-8.1 g/dL	6.5[a]	6.1[a]	6.1[a]	7.1
Albumin	4.1-5.1 g/dL	3.4[a]	3.0[a]	3.3[a]	4.0[a]
C-reactive protein	0-0.14 mg/dL	2.70[a]	1.52[a]	< 0.02	0.26[a]
ESR	< 15 mm/hour	46[a]	41[a]	3	1
Plasma glucose	70-109 mg/dL	258[a]	449 (F)[a]	88 (F)	106
HbA1c	4.6%-6.2%	7.3[a]	8.0[a]	7.2[a]	5.9
Amylase	44-132 U/L	250[a]	200[a]	214[a]	77
Lipase	13-55 U/L	n.t.	448[a]	134[a,b]	46
CA 19-9	0-36.9 U/mL	44.9[a]	39.4[a]	26.9[b]	n.t.
PR3-ANCA	< 3.5 U/mL		16.3[a]		
MPO-ANCA	< 3.5 U/mL		< 1.0		
GAD-Ab	< 1.5 U/mL		< 5.0		
C-peptide	0.8-2.5 ng/mL		3.1[a]		
Urine C-peptide	8-155.2 μg/day		116		
Urinary ketone bodies	-		-		

HD: hospital days, F/U: follow-up after discharge, LDL: low density lipoprotein, ESR: erythrocyte sedimentation rate, F: fasted, HbA1c: hemoglobin A1c, CA 19-9: cancer antigen 19-9, PR3-ANCA: proteinase 3 antineutrophil cytoplasmic antibodies, MPO-ANCA: myloperoxidase antineutrophil cytoplasmic antibody, GAD: glutamic acid decarboxylase, n.t.: not tested.
[a]Out of reference range.
[b]29HD.

cating AIP (Fig. 2A-2C). IgG4 36.0 mg/dL (reference 4.5-117) was normal. These findings led to a tentative diagnosis of type 2 AIP. Two anti-platelet agents, aspirin and clopidogrel, hampered execution of endoscopic ultrasonographic fine-needle aspiration biopsy from the pancreas. Oral prednisolone (40 mg/day) was initiated for the treatment of both UC and AIP on the 15th hospital day (Fig. 1). Lispro and glargine were adjusted to 17-19-16-0 units and 0-0-0-26 units, respectively (Fig. 1). Diarrhea gradually became formed stool after prednisolone administration. Ultrasonography indicated improvement in the swelling of the pancreas. Lipase decreased from 448 to 134 U/L (Table 1, Fig. 1). His condition improved except for a small amount of blood ahead of the first defecation. He was discharged after 5 weeks of hospitalization. C-reactive protein and erythrocyte sedimentation rate normalized, but abnormalities including amylase, lipase, and albumin persisted (Table 1). He received dietary guidance from a qualified dietitian and was advised to continue with the PBD after discharge.

Because the small amount of blood ahead of the first defecation persisted, colonoscopy was performed in the beginning of June. It revealed remission in the colon, but mild inflammation in the rectum (Mayo Clinic Endoscopic Subscore 1). Mesalamine enema resulted in disappear-

ance of the blood. Prednisolone was tapered off at the end of October 2022. CT in April 2023 revealed improvement in swelling of the pancreas (Fig. 2D). Probable type 2 AIP was ultimately diagnosed. The last medication was as follows: oral mesalamine for UC, metformin 500 mg and linagliptin 5 mg, and insulin (lispro 8-6-4-0 units and glargine 0-0-0-5 units/day). The latest laboratory findings during the 18 months since discharge are presented in Table 1. There was no unanticipated adverse event during the clinical course.

His plant-based diet score (PBDS), which evaluates adherence to PBD for Japanese patients with IBD (a higher PBDS indicates greater adherence to PBD) [3], was 15 before admission and 35 during hospitalization. It was 26 13 months after discharge.

The present study protocol was reviewed and approved by the institutional review board of Akita City Hospital (Reg. No. 15-2015). Informed consent was submitted by all subjects when they were enrolled. This is a clinical trial registered at the University Hospital Medical Information Network (http://www.umin.ac.jp), number UMIN000019061.

Fig. 1. Timeline of case. AMI: acute myocardial infarction, UC: ulcerative colitis, AIP: autoimmune pancreatitis, US: ultrasonography, CT: computed tomography, MRCP: magnetic resonance cholangiopancreatography, PS: prednisolone, Lis: lispro, Gla: glargine, Alo/Met: alogliptin/metformin combination tablet, Glim: glimepiride, HbA1c: hemoglobin A1c (reference 4.6%-6.2%), Amy: amylase (reference 44-132 U/L), Lip: lipase (reference 13-55 U/L).

DISCUSSION

There were no symptoms of AIP in our case despite 98% of the cases in the literature exhibiting symptoms of acute pancreatitis, abdominal pain, or jaundice [6]. In our case, diabetologist's recognition of rapid deterioration of plasma glucose and HbA1c led to a diagnosis of probable AIP. Otherwise, AIP would have been undiagnosed. Type 2 AIP was reported to evolve toward diabetes in 12% of cases [6], but our case was already affected by T2D. Meticulous glycemic control against high plasma glucose due to AIP as well as due to side effects of prednisolone was needed in our case.

Three diseases occurred in sequence in almost 2 months: AMI, UC, and AIP. The patient had been affected by risk factors for AMI: hypertension for almost 30 years and T2D for more than 3 years. He quit smoking after developing AMI. Discontinuance of smoking is known to be a risk factor for UC. Onset of UC occurs most frequently within 2 years after smoking cessation. In the literature, there are case reports of onset of UC 1 or 2 months after quitting smoking. In the present case, UC occurred 2 months after cessation. It is uncertain to what extent the smoking cessation was responsible for the onset of UC in our case.

Basic medicine recently unraveled the interplay between diet, gut microbiota, microbial metabolites, and health/disease [7-9]. The principal pathophysiology in CMD is reduced gut microbial diversity (dysbiosis), reduced short chain fatty acid levels including butyrate, immune dysregulation, intestinal barrier dysfunction, metabolic endotoxemia, increase in inflammatory mediators, and chronic inflammation [8]. This phenomenon is identical in IBD [9]. Multidisciplinary
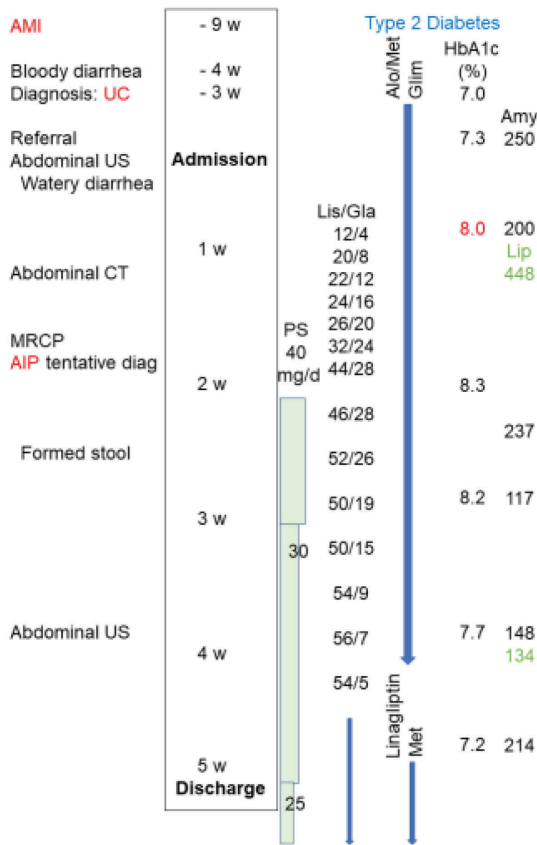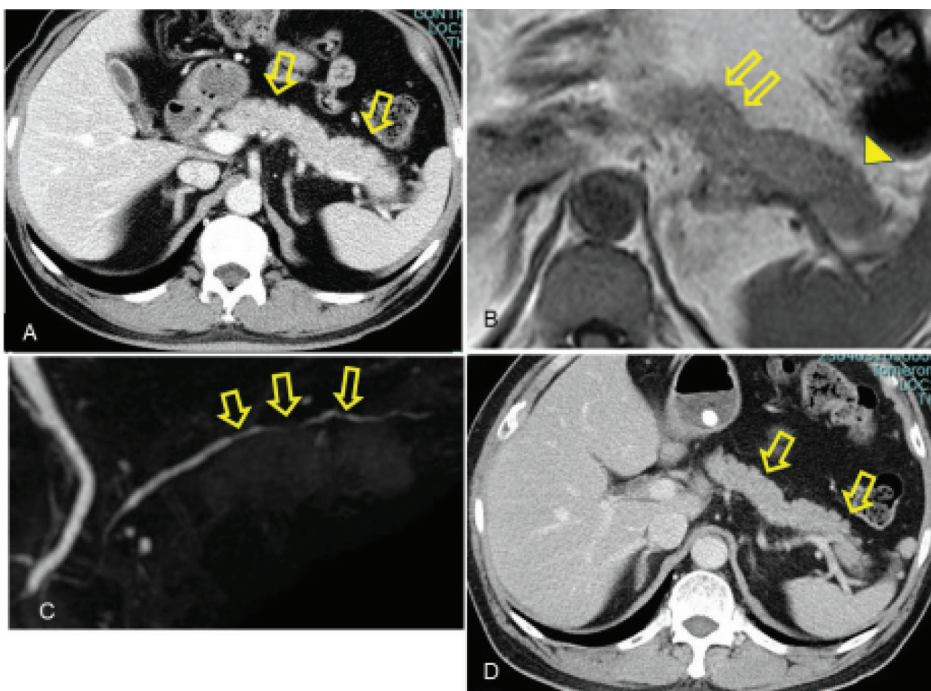

Fig. 2. (A) Computed tomography, (B, C) a magnetic resonance cholangiopancreatography before therapy, and (D) computed tomography 1 year later. Enlargement of the pancreas (arrows in A, arrowhead in B) with a peripheral rim (arrows in B) and uneven staining of the main pancreatic duct (arrows in C) indicating narrowing were observed. The enlargement had disappeared 1 year later (arrows in D).

studies demonstrated that the current (westernized) diets are pro-inflammatory, while PBD is an anti-inflammatory [3,7]. Apart from diet, in IBD, there are susceptible genes related to epithelial barrier function (*CDH1*, *ECM1*, *GNA12*, *HNF4A*, and *LAMB1*) and genes susceptible to both T2D (*CDKAL1*, *CAPN10*, *GCKR*, *HNF4A*, and *THADA*) and coronary artery disease (*SMAD3*) [10]. The former might render the epithelial layer permeable to lipopolysaccharides. *HNF4A* is common to both UC and T2D. At present, the extent to which these genetic factors contribute to the association between chronic common diseases and IBD is not fully understood. Increased risk of T2D, AMI, and NAFLD in IBD has been reported [4,5]. Because diet-induced gut microbial dysbiosis is closely related to the pathophysiology of CMD, manipulation targeting gut microbiota via diet, probiotics, prebiotics, synbiotics, or antibiotics has been investigated. PBD is already known to prevent chronic diseases and is recommended to the public [1]. PBD was effective for IBD [3]. The authors hope that the present patient adheres to PBD and to prevent further deterioration of his diseases.

In conclusion, we reported a case of simultaneous onset of UC and type 2 AIP 2 months after AMI in a patient with T2D. Our case was an illustrative case of the association between CMD and IBD due to current unhealthy diets and shared pathogenesis. From now on such associated cases of IBD and CMD will appear more frequently. Greater appreciation of the role of diet in health/disease is needed to halt the global increase of CMD and IBD.

NOTES

- **ORCID**
  Mitsuro Chiba, https://orcid.org/0000-0001-6382-0047
  Takeshi Miura, https://orcid.org/0009-0007-0217-0395
  Hisanori Matsuzawa, https://orcid.org/0009-0003-5619-5935
  Tsuyotoshi Tsuji, https://orcid.org/0000-0003-1447-1287
  Haruhiko Tozawa, https://orcid.org/0009-0006-6541-859X
  Akira Zeniya, https://orcid.org/0009-0000-2400-3490
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