

[ CASE REPORT ]

## Granulocyte and Monocyte Adsorptive Apheresis for Ulcerative Colitis in a Patient with Low Bone Mineral Density Due to Fanconi-Bickel Syndrome

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### Abstract:

Systemic steroid is required for the exacerbation of ulcerative colitis (UC), although its administration should be avoided in patients with a low bone mineral density (BMD) exacerbated by side effects of steroids. We herein report the successful induction of remission in an UC case with a low BMD due to Fanconi-Bickel syndrome-or glycogen storage disease type XI-using granulocyte and monocyte adsorptive apheresis (GMA). For a 43-year-old woman with a BMD of 50% the young adult mean, GMA was performed 2 times a week for a total of 10 times. GMA might be a steroid-free treatment option for UC patients with a low BMD.

**Key words:** ulcerative colitis, granulocyte and monocyte adsorptive apheresis, bone density, Fanconi-Bickel Syndrome

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### Introduction

Fanconi-Bickel syndrome (FBS), also known as glycogen storage disease type XI, is a special form of liver-type glycogen storage disease. It is a rare autosomal recessive metabolic disorder characterized by an impaired metabolism of glucose and galactose and the accumulation of glycogen in the liver and kidneys (Fanconi nephropathy), leading to decreases in bone mineral density (BMD) and proximal renal tubular dysfunction (1). The disease was first reported by Fanconi and Bickel in 1949 (2). In 1997, the gene for the transport protein glucose transporter 2 (*GLUT2*) was identified as the gene responsible for this disease (3).

Ulcerative colitis (UC) is a refractory, chronic inflammatory bowel disease of unknown origin that forms a chronic inflammatory lesion in the large intestine. Systemic steroid play important roles as the first-line drug in induction ther-

apy at the time of UC exacerbation (4). However, the first-line drug for use in induction therapy is unclear in cases of UC developing in patients who have difficulty receiving steroid administration because of underlying conditions, such as glycogenosis, that result in a low BMD and impaired metabolism.

We herein report a patient with UC complicated with FBS. The patient had a markedly decreased BMD. We selected granulocyte and monocyte adsorptive apheresis (GMA) with Adacolumn<sup>®</sup> as our first choice of treatment and successfully performed remission induction therapy. This patient had mild renal dysfunction in addition to a low BMD. Salazosulfapyridine was useful without inducing the further exacerbation of renal dysfunction. To our knowledge, there have been no reports of remission induction therapy in UC cases with FBS.

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**Figure 1.** Findings of plain abdominal computed tomography of the patient on admission. The wall of the intestinal tract thickened from the rectum to the transverse colon. (A) Transverse colon, (B) sigmoid colon, and (C) rectum.

**Table.** Blood Test and Fecal Culture Results on Admission.

List	Standard value	Value
WBC ( $\times 10^3/\mu\text{L}$ )	(3.2-8.5)	6.0
RBC ( $\times 10^4/\mu\text{L}$ )	(370-490)	293
Hemoglobin (g/dL)	(11.3-14.8)	9.3
Hematocrit (%)	(34-45)	29.3
Plt ( $\times 10^3/\mu\text{L}$ )	(160-370)	374
ESR (mm/h)	(3-15)	66
CRP (mg/dL)	(less than 0.30)	0.44
TP (g/dL)	(6.1-8.2)	6.2
Albumin (g/dL)	(3.9-5.0)	2.5
TB (mg/dL)	(0.05-1.15)	0.26
AST (IU/L)	(5-46)	12
ALT (IU/L)	(4-51)	6
LDH (IU/L)	(100-225)	160
Glu (mg/dL)	(76-110)	76
BUN (mg/dL)	(5.5-23.1)	6.2
Creatinine (mg/dL)	(0.6-0.9)	1.02
eGFR (mL/min/1.73 m <sup>2</sup> )	(90 or more)	47.7
Na (mEq/L)	(136-146)	136
K (mEq/L)	(3.5-4.9)	3.8
Cl (mEq/L)	(96-110)	102
IP (mg/dL)	(2.4-4.3)	2.2
C7-HRP	Positive	
The number of positive counts		1/50,000WBC
Fecal culture		
Common bacterium	Negative	
Acid-fast bacterium	Negative	

WBC: white blood cell, RBC: red blood cell, Plt: platelets, LD: lactate dehydrogenase, TB: total bilirubin, TP: total protein, Glu: glucose, eGFR: estimated glomerular filtration rate, IP: inorganic phosphorus, C7-HRP: cytomegalovirus antigenemia

## Case Report

We conducted this study in compliance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of Saiseikai Shigaken Hospital. Written informed consent was obtained.

A 43-year-old woman was admitted to our hospital due to

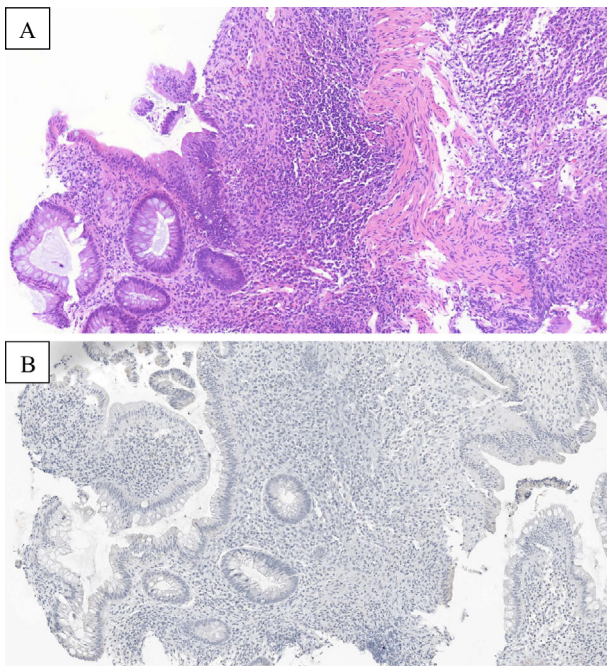
hematochezia, lower abdominal pain, and diarrhea. She had been diagnosed with FBS at seven years old. She had no family history, and no other family members had glycogen storage disease. At the initial assessment upon admission, she had an apparent growth disorder. Her height and weight were 117 cm and 28 kg, respectively.

Plain abdominal computed tomography showed marked wall thickening from the rectum to the transverse colon (Fig. 1). Her blood examinations also revealed high levels of inflammatory response markers [erythrocyte sedimentation rate (ESR), 66 mm/h; C-reactive protein (CRP), 0.44 mg/dL]. The nutritional status was poor, and the serum albumin level was 2.5 g/dL. The creatinine value was 1.02 mg/dL. Mild renal impairment was confirmed with an estimated glomerular filtration rate of 47.7 mL/min/1.73 m<sup>2</sup>. Several days after hospitalization, the patient was found to be positive for cytomegalovirus (CMV) antigens (Table). However, the number of positive cells was 1/50,000 white blood cells (WBCs), and no CMV-positive cells were observed by CMV immunohistochemistry staining (Fig. 2).

Colonoscopy revealed a continuously inflamed mucosa from the rectum to the transverse colon (Fig. 3). The ulcerative colitis endoscopic index of severity (UCEIS) (5) was 5, and the Mayo endoscopic score for ulcerative colitis (MES) (6) was 2.

The biopsy specimens taken during colonoscopy showed pathologic findings specific to UC. UC was considered based on the pathologic and endoscopic findings. However, infectious colitis and CMV colitis associated with UC could not be ruled out, although the possibility was deemed low based on the number of CMV antigen-positive cells and the results of immunohistochemistry staining. Thus, the patient was initially treated with both antibiotics and antivirals. Unfortunately, she continued to have frequent diarrhea.

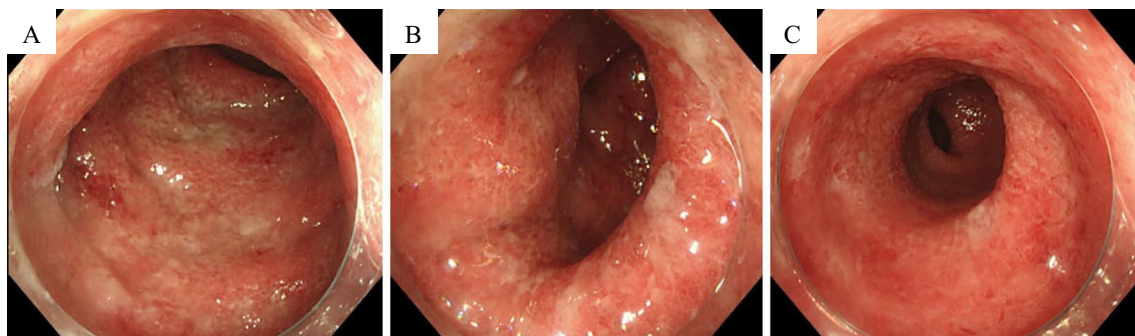
The patient was started on salazosulfapyridine (3,000 mg/day), which can be used regardless of the renal disorder while preventing further deterioration of the renal function. The UC was categorized as total colitis type [Lichtiger Clinical Activity Index (CAI)=11 (7)]. Although the administration of mesalazine was initiated, the frequency of bloody stools and diarrhea did not improve. The patient was started



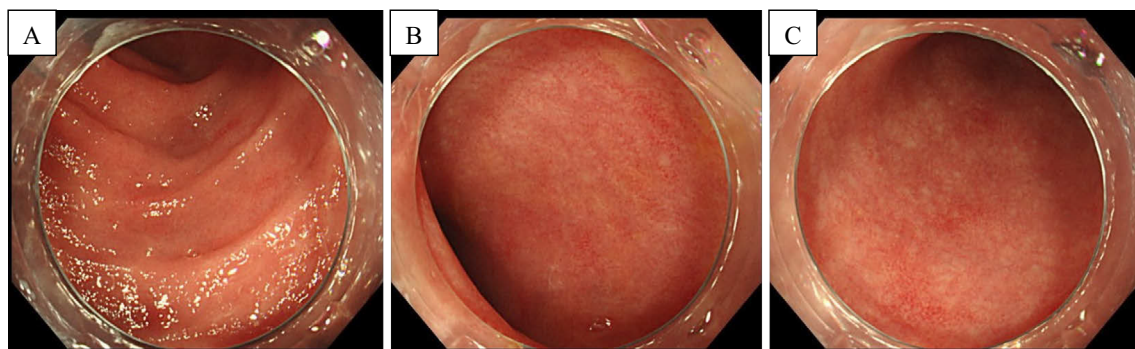
**Figure 2.** The histological images of (A) Hematoxylin and Eosin staining and (B) immunohistochemistry staining of the large intestine (Scale bars represent 100  $\mu$ m). No CMV-positive cells were observed by CMV immunohistochemical staining. CMV: cytomegalovirus

on GMA therapy using Adacolumn<sup>®</sup>. Steroid therapy was discouraged because of the patient's low BMD. Her BMD of the greater trochanter of the femur measured by dual energy X-ray absorptiometry was 0.377 g/cm<sup>2</sup>, which was 50% of the young adult mean. GMA therapy was performed twice weekly. It was important for remission induction to succeed as quickly as possible because a patient with FBS syndrome can easily develop hypoglycemia when meal quantities and caloric intakes are decreased. In fact, the patient manifested hypoglycemic symptoms whenever the meal quantities were limited (when the daily dietary calorie intake was  $\leq$ 1,200 kcal).

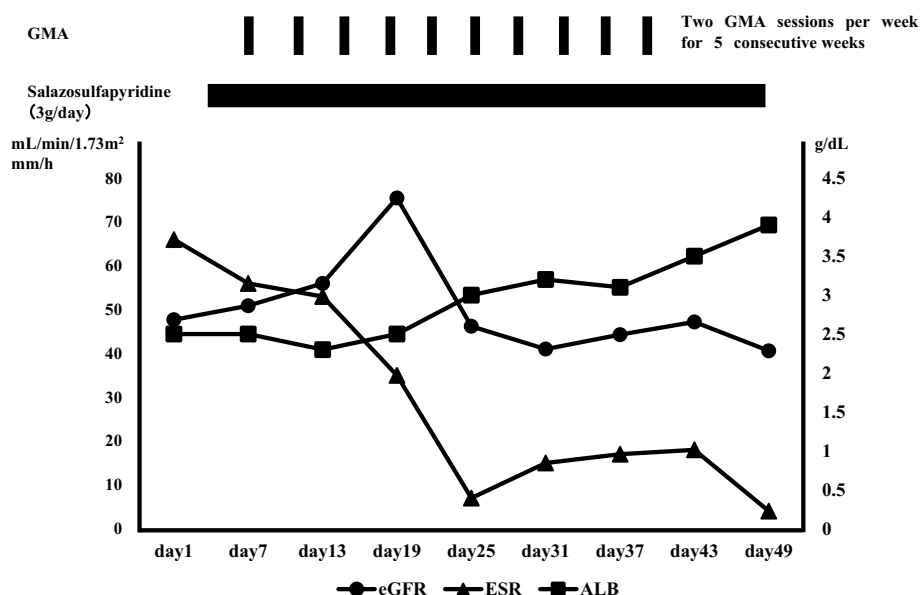
After GMA therapy was administered 4 times, the levels of her inflammatory response markers improved markedly (CRP, 0.01 mg/dL; ESR, 7.0 mm/h; CAI 3). She tested negative for CMV antigenemia after the fourth GMA. To evaluate the healing of the intestinal mucosa, colonoscopy was performed after the eighth GMA. The endoscopic findings showed that intestinal mucosal healing had almost been achieved (Fig. 4). UCEIS did not go down to 0 but did decrease to 1 (8), and in MES, it was 1 or 0. After receiving GMA therapy a total of 10 times, the patient's serum albumin levels rose to 3.9 g/dL, and she was discharged with improvement (Fig. 5). One year has passed since the completion of GMA therapy and salazosulfapyridine therapy



**Figure 3.** Endoscopic findings of the patient on admission. Total colonoscopy was performed, and the patient was diagnosed with UC. (A) Transverse colon, (B) sigmoid colon, and (C) rectum. UC: ulcerative colitis



**Figure 4.** Endoscopic findings of the patient after the eighth GMA. Total colonoscopy was performed, and intestinal mucosal healing had almost been achieved. (A) Transverse colon, (B) sigmoid colon, and (C) rectum. GMA: granulocyte and monocyte adsorptive apheresis



**Figure 5.** Clinical course from hospitalization to discharge. GMA: granulocyte and monocyte adsorptive apheresis, eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate, ALB: albumin

alone; this patient has had no recurrence.

## Discussion

GMA was found to be useful as remission induction therapy for patients with underlying disorders who have a low BMD and cannot be treated with steroids. In addition, GMA and salazosulfapyridine were useful without causing the further exacerbation of renal dysfunction.

GMA was found to be useful for the present UC patient with a low BMD. There have been no reports of GMA exacerbating BMD. Furthermore, we have found no reports of GMA affecting glycogen storage disease in adults. The use of glucocorticoids is known to be a risk factor for a low BMD in patients with UC (9).

Patients with inflammatory bowel disease (IBD) are reported to have a higher frequency of osteoporosis and bone loss than healthy subjects. Furthermore, osteoporosis is recognized as an extraintestinal complication experienced by patients with IBD (10, 11, 12). Therefore, it is important to treat UC while considering patients' BMD.

A multicenter, retrospective study was recently conducted to identify patients who responded well to adsorptive granulomonocytapheresis (13). The authors found that the predictors of a favorable response to GMA were age  $\leq 60$  years old, UC duration  $< 1$  year, Mayo endoscopic sub score 2 (vs. 3), and steroid- and biological agent-naïve UC.

At present, there is no consensus concerning the treatment of choice for UC patients with glycogen storage disease. The patient in this case report was  $< 60$  years old. Her UC duration was also  $< 1$  year. Her Mayo endoscopic sub score was 2 (vs. 3), and her UC was considered to be steroid- and biological agent-naïve. Thus, in patients with a low BMD,

GMA may be an effective treatment, especially when steroid therapy must be avoided.

GMA and salazosulfapyridine were useful for treating this case without causing further exacerbation of renal dysfunction. Mesalazine is frequently prescribed for remission therapy and for maintenance therapy in patients with UC. Its careful administration is required for patients with moderate renal dysfunction. In addition, the administration of mesalazine is contraindicated in patients with severe renal dysfunction; therefore, we administered salazosulfapyridine, although the renal dysfunction did not worsen. According to the Japanese CKD guidelines (14), there is no need to reduce the dose of salazosulfapyridine, even when it is administered to patients with an impaired renal function; therefore, salazosulfapyridine was used in this case.

CMV reactivation is also an important issue for UC. The present patient was positive for CMV antigens. The CMV antigenemia assay has a high specificity and low sensitivity for moderate-to-severe UC. It must be recognized that peripheral blood reactivation does not necessarily reflect CMV reactivation in the intestinal tract (15). The gold standard for diagnosing CMV infections is a histological examination in combination with hematoxylin and eosin staining and immunohistochemical staining. However, the CMV positivity rate depends on the number of biopsy tests performed and the location where the biopsy was performed (16). We must therefore be careful when interpreting the results.

In this case, whether or not CMV colitis was present was unclear. GMA has been reported to have little effect on CMV reactivation, as it has no direct effect on the local immune system (17, 18). Therefore, GMA is effective as remission induction therapy for UC patients with a history of

CMV infection. Even if it is not possible to determine if CMV infection is present or not at the onset of UC, GMA may be effective as remission induction therapy for UC patients.

Although it is rare to treat UC patients with a low BMD and a renal function that has been impaired by a special underlying disease, as in the present case, the chances of encountering cases similar to this case are expected to increase in the future.

The above reasons are why UC has been considered a disease that develops at a young age, although in recent years, the number of cases that develop at an older age has been increasing (19-22), and the number of cases with exacerbation in old age is expected to increase with the aging of the population. There will thus likely be more opportunities to select and administer appropriate remission induction therapy when the symptoms in UC patients with a low BMD due to old age or underlying disease or with renal function worsen.

GMA was found to be useful as remission induction therapy for patients with underlying disorders with a low BMD who cannot be treated with steroids. In addition, GMA and salazosulfapyridine were useful for treating UC without inducing further exacerbation of renal dysfunction.

Our findings may be applicable to not only UC patients with FBS as the underlying disease, similar to the present case, but also to those with other glycogen storage diseases as the underlying disease or with diseases other than glycogen storage diseases that induce a reduction in the BMD. However, our findings are from a single case, so it is necessary to accumulate more cases to investigate whether or not GMA is a suitable first choice for remission induction therapy in UC patients with a low BMD.

In conclusion, our experience with the current case suggests that GMA may be useful as remission induction therapy for patients with underlying disorders who have a low BMD and who cannot be treated with steroids. We recommend further investigations be conducted to establish a detailed consensus concerning the appropriate timing and patient selection for GMA therapy.

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

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