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Infliximab- and Immunosuppressant-Resistant Crohn's Disease Successfully Treated with Adsorptive Granulocyte Apheresis Combined with Prednisolone

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Key Words
Adsorptive granulocyte apheresis · Infliximab · Prednisolone · Azathioprine · Crohn's disease

Abstract
Activated granulocytes, monocytes, and platelets appear to be closely involved in active Crohn's disease (CD). Adsorptive granulocyte apheresis (GCAP) is a new treatment for inflammatory bowel disease. GCAP was used to treat a 23-year-old female patient with CD resistant to both infliximab (IFX) and azathioprine (AZA). At 16 years of age, the patient underwent a partial ileal resection for peritonitis caused by perforative ileitis. On pathological examination of the resected specimen, the diagnosis was CD. Mesalazine was started, but the patient did not comply with therapy. She was admitted to our hospital again in 2007 due to an acute exacerbation. IFX induction therapy was started. The combination of both AZA daily and IFX every 8 weeks was continued as maintenance therapy. However, she developed severe abdominal pain in September 2009. Computed tomography revealed ileitis and ascending colitis, and blood tests showed high inflammatory response marker levels. She was considered to have IFX- and AZA-resistant CD. Initial intravenous steroid therapy did not result in any improvement. Therefore, weekly GCAP therapy was given for 5 weeks, which immediately improved the inflammatory response markers. GCAP combined with prednisolone could be effective for IFX- and AZA-refractory CD.

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Introduction

Inflammatory bowel disease (IBD) comprises a group of cryptogenic diseases of the intestine with long-standing chronic inflammation characterized by repeated exacerbations and remissions. Steroid treatment is still a cornerstone of medical treatment for IBD, such as ulcerative colitis and Crohn's disease (CD). Unfortunately, IBD patients who are treated with steroids sometimes develop steroid-dependent or steroid-resistant conditions. Immunosuppressants, such as azathioprine (AZA) and 6-mercaptopurine, and new biological drugs, such as infliximab (IFX), are considered effective treatments in inducing disease remission and steroid-free clinical remission. Although these medications are key treatments for IBD, some patients are refractory or intolerant to them, and it is very difficult to control their disease activity. Activated granulocytes, monocytes, and platelets are known to play important roles in active IBD. Adsorptive granulocyte apheresis (GCAP) to reduce the level of activated peripheral blood leukocytes in patients with ulcerative colitis has significant clinical efficacy and suppresses pro-inflammatory cytokines produced by peripheral blood leukocytes. These actions should directly reduce leukocytes and granulocytes related to inflammation and induce remission in patients with active CD. Some investigators have postulated that GCAP therapy might be effective for inducing remission and for treating patients with refractory CD. Therefore, GCAP and steroid combination therapy was tried in the following CD case who was refractory to IFX and AZA.

Case Report

A 23-year-old woman with CD was admitted to our hospital for the treatment of lower abdominal pain. At the age of 16 years, she underwent an ileo-cecal resection because of peritonitis caused by perforation thought to be due to acute appendicitis. CD was finally diagnosed based on the presence of the pathological characteristics of CD in the resected intestine. Mesalazine was started for the CD, but the patient did not comply with this therapy. She was admitted to our hospital again in 2007 (5 years after her last examination) due to an acute exacerbation. Three infusions of IFX (5 mg/kg) were administered as induction therapy, and further doses were repeated every 8 weeks as maintenance therapy. However, she had severe abdominal pain and frequent diarrhea again in February 2009, which was thought to be an acute exacerbation of CD based on physical examination and laboratory data. Initially, the interval of IFX administration was shortened from 8 to 6 weeks, and she recovered from these symptoms. Three months later, she had occasional abdominal pain again, and she was thought to have developed tachyphylaxis to IFX; therefore, an immunosuppressant (AZA 0.5 mg/kg) was started. Unfortunately, severe abdominal pain developed again in September 2009. Non-enhanced abdominal computed tomography (CT) showed marked wall thickness and fluid collection in the anastomosis (fig. 1). Blood examination also disclosed high inflammatory response marker levels (erythrocyte sedimentation rate [ESR] 37 mm/h, C-reactive protein [CRP] 4.23 mg/dl). The CD activity index (CDAI) had also increased to 255.

Oral intake was stopped, and intravenous hyperalimentation was given from the start of admission. Intravenous prednisolone (40 mg/day, 0.8 mg/kg) was also infused because her CD was considered to be severely active. However, her condition did not respond to intensive steroid therapy for 1 week. Weekly GCAP therapy was then given for 5 weeks. Once GCAP therapy was started, her inflammatory response marker levels immediately and completely improved (CRP 0.22 mg/dl, ESR 9 mm/h; CDAI 21). Abdominal CT, which was performed 1 week after the second GCAP, also showed marked improvement of wall thickness and fluid collection in the anastomosis. To evaluate the intestinal mucosal healing, balloon enteroscopy was performed after the third GCAP. The enteroscopic findings showed destroyed ileo-cecal valves, despite the absence of active ulcers or erosions (fig. 2). A fibrous stricture of the anastomosis was considered to be a non-responsive lesion to the steroid and

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GCAP treatment. Therefore, an ileo-cecal resection was performed to remove this stricture. Since the operation, she has been well.

Discussion

IFX is considered to be a key therapy for inducing and maintaining remission in patients with CD [1, 2]. Regularly scheduled IFX therapy for CD consists of 3 infusions of IFX (5 mg/kg) to induce remission, and further doses are repeated every 8 weeks [2]. High-dose IFX therapy or a shorter period of scheduled IFX therapy is sometimes required when the effects of IFX are weakened because of the development of antibodies to IFX. Immunosuppressants such as AZA and 6-mercaptopurine are also widely used as CD maintenance therapy. Recently, the SONIC study reported that IFX and AZA combination therapy induced higher rates of corticosteroid-free clinical remission and mucosal healing compared to IFX monotherapy or AZA monotherapy [3]. This case maintained remission with IFX therapy initially, but then developed frequent diarrhea and abdominal pain despite receiving IFX every 8 weeks as maintenance therapy. The addition of an immunosuppressant to IFX was not effective for her acute exacerbation. Although intravenous prednisolone had been administered for 1 week to relieve her symptoms, she showed no evidence of recovery. Therefore, another therapy was needed to control her inflammatory reaction. We decided to use GCAP therapy because it has been reported to be a novel therapy for CD that can reduce the inflammatory response. From the start of GCAP therapy, her symptoms and inflammatory response immediately and completely improved. Abdominal CT, which was performed 1 week after the second GCAP, also showed marked improvement of wall thickness and fluid collection in the anastomosis. The balloon enteroscopy performed 1 week after the third GCAP also disclosed no active ulcers or erosions other than the destroyed ileo-cecal valves. The patient's clinical course is summarized in **fig. 3**.

In general, active CD lesions involve activated granulocytes, monocytes, and platelets. GCAP is an extracorporeal apheresis technique in which a specialized column selectively traps peripheral activated granulocytes and monocytes [1]. This therapy is expected to suppress and stop the immunological response in the active phase, as in an acute exacerbation. GCAP is a novel therapy for IBD, and it was first reported by Shimoyama et al. in 2001 [1]. GCAP is performed with a unique immuno-adsorption column, Adacolumn® (Japan Immuno-Research Co. Ltd., Gunma, Japan). The Adacolumn® has a capacity of 335 ml, filled with 220 g of 2 mm diameter cellulose acetate beads as the column adsorptive carriers. The carriers adsorb about 65% of granulocytes, 55% of monocytes, and a small fraction of lymphocytes (FcγR and complement receptor-bearing leucocytes) [4]. GCAP therapy obviously suppresses the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-8) by circulating peripheral blood leucocytes [1]. GCAP therapy was well tolerated, and no severe side effects were reported [4–10]. Recently, some investigators have postulated that patients with refractory CD might respond to a reduction of granulocytes and monocytes with GCAP. Both Kusaka et al. [7] and Fukuda et al. [6] reported in 2004 that GCAP is effective for inducing remission and improving quality of life in patients with active CD that is refractory to conventional therapies such as mesalamine, prednisolone, metronidazole, and nutritional therapy. Fukuda et al. [6] also reported

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that 11 of 21 active CD patients (52.4%) responded to GCAP, 6 with clinical remission and 5 with significant improvement. At present in Japan, GCAP therapy for CD is performed as 5 apheresis treatments over 5 weeks (once a week). Some papers have also reported that GCAP is effective for patients with rheumatoid arthritis [11], pyoderma gangrenosum [12], pustular psoriasis [13], and severe alcoholic hepatitis.

In the present case, prednisolone therapy did not completely relieve the patient's symptoms, but levels of inflammatory response markers, such as CRP, ESR and CDAI, were partially improved. On the other hand, her clinical findings and CT findings immediately improved when GCAP therapy was combined with prednisolone therapy. Therefore, we consider that, except for a fibrous stricture, GCAP and prednisolone combination therapy was an effective treatment for active CD in our patient. GCAP combined with prednisolone could be effective for IFX- and AZA-refractory CD.

Disclosure Statement

The authors have no funding or conflicts of interest to disclose.

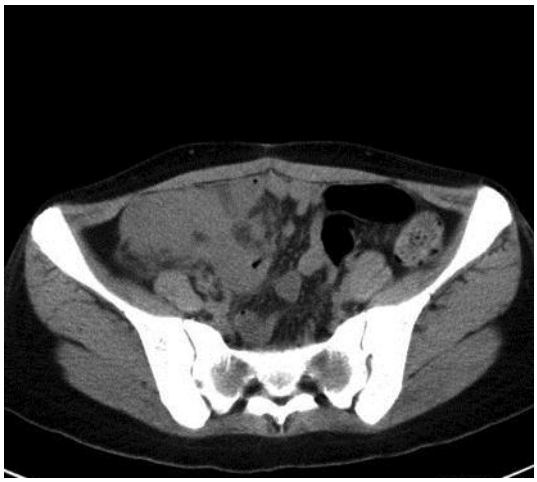

Fig. 1. Non-enhanced abdominal CT on admission showed marked wall thickness and fluid collection in the anastomosis.

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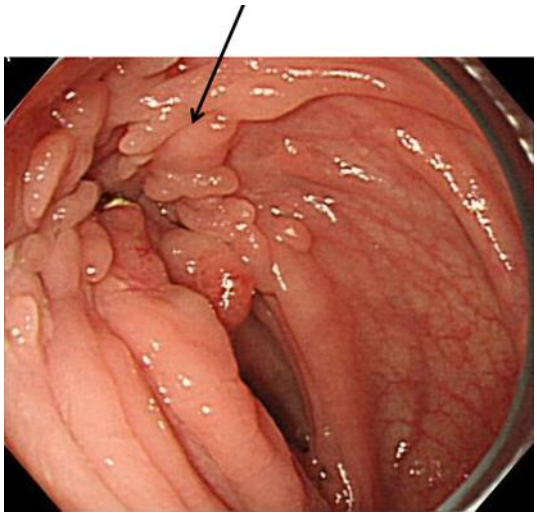

Fig. 2. Balloon enteroscopy was performed 1 week after the third GCAP therapy to evaluate intestinal mucosal healing. It showed no active ulcers or erosions, except for the destroyed ileo-cecal valves.

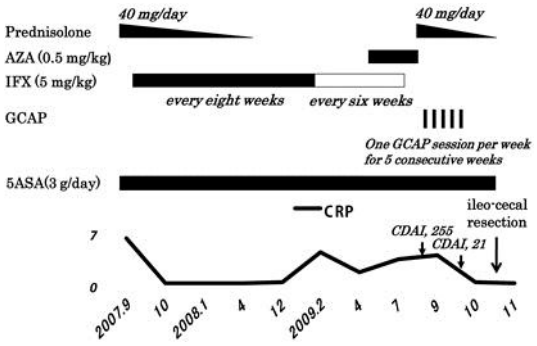

Fig. 3. Clinical course.

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