Pyoderma Gangrenosum with Ulcerative Colitis Successfully Treated by the Combination of Granulocyte and Monocyte Adsorption Apheresis and Corticosteroids

Masashi Ohno¹, Shigeki Koyama¹, Mariko Ohara¹, Kazumi Shimamoto¹, Yu Kobayashi¹, Fumiyasu Nakamura¹, Kazuki Mitsuru³ and Akira Andoh²

Abstract

A 36-year-old woman was admitted to our hospital due to swelling and redness of the left lateral malleolus and dorsum of the left foot with severe pain, with a flare-up of ulcerative colitis (UC). A pathologic examination by skin biopsy led to a diagnosis of pyoderma gangrenosum (PG). She was treated with the intravenous administration of prednisolone (60 mg/day), and granulocyte and monocyte adsorption apheresis (GMA) was performed twice-a-week for 5 weeks. This treatment dramatically improved both the skin and colonic mucosal lesions. These results suggest that a combination of GMA and corticosteroids might be recommendable to induce the remission of serious PG complicated with UC.

Key words: ulcerative colitis, pyoderma gangrenosum, granulocyte and monocyte adsorption apheresis

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Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease, is associated with a variety of extraintestinal manifestations that sometimes lead to greater morbidity than the underlying intestinal disease (1, 2). Previous studies have reported that as many as 30% of patients with IBD have at least one extraintestinal manifestation, such as pyoderma gangrenosum (PG), erythema nodosum, polyarthritis, or iritis (2-4).

PG is a rapidly progressing skin lesion consisting of painful and necrotic areas of ulceration with an irregular margin (5). The diagnosis of PG involves excluding other causes of cutaneous ulcers, such as infectious disease, malignancy and vasculitis. Approximately half of PG patients are found to show complications of systemic disease (6), and PG has been reported to occur in about 2% of patients with IBD (6, 7). Although the precise pathogenesis of PG remains unclear, the activation of neutrophils has been suggested to play an important role (5).

Case Report

A 36-year-old woman who was diagnosed with UC (pancolitis type) almost 15 years previously was admitted to our hospital due to swelling and redness of the left lateral malleolus and the dorsum of the left foot with severe pain (Fig. 1). She also complained of a flare-up of UC with abdominal pain and frequent bloody diarrhea (over 20 times/day). She had no history of hospital admission and remission had been maintained by oral salazosulfapyridine (SASP: 4.5 g/day) with the occasional use of corticosteroid enemas when a mild exacerbation of symptoms occurred.

The laboratory data on admission were as follows: white blood cell count, 8,400/μL (normal, 4,000-8,500/μL); eryth-
The exacerbation of UC was confirmed by sigmoidoscopy, showing an edematous mucosa with a large mucosal defect and easy bleeding (Matts’ endoscopic grading 4) (Fig. 2A). T2 weighted magnetic resonance imaging (MRI) suggested a subcutaneous abscess of the left foot (Fig. 3).

The skin lesions of the left foot were initially suspected to represent acute bacterial cellulitis, but administration of antibiotics and surgical drainage proved ineffective. The bacterial cultures of the skin lesions showed no results. The skin lesions rapidly progressed to form ulcers within a couple of days (Fig. 1). The results of a skin biopsy revealed sterile neutrophilia of the entire dermis and no evidence of malignancy, vasculitis or infectious disease, leading to a diagnosis of PG.

Since the disease activities of UC and PG were severe, we initiated the intravenous administration of prednisolone at 60 mg/day, and GMA with the Adacolumn (JIMRO, Takasaki, Japan) was performed twice-weekly for 5 weeks. At each GMA session, blood was drained from the cubital vein of one arm, circulated through the column, and returned to the cubital vein of the other arm. The flow rate was 30 mL/min and the duration of each session was 60 minutes. After the 3rd session of GMA, the patient’s stool frequency decreased from over 20 times per day to around 5 times per day and her bloody stool disappeared. The patient’s skin lesions also improved dramatically, and pain was markedly alleviated after the 3rd session of GMA. After the 10th session of GMA, the ulcers became crusted and dried up (Fig. 1). In addition, sigmoidoscopy revealed that colonic lesions were markedly improved (Fig. 2B). The patient’s serum CRP level was also improved by the combination of

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GMA and corticosteroids (Fig. 4). No adverse effects of GMA were encountered. The dosage of was gradually tapered. The administration of intravenous prednisolone (60 mg/day) was continued for one week and followed by oral prednisolone (50 mg/day) for one week. The oral prednisolone dosage was reduced to 20 mg/day by a 10 mg reduction every 2 weeks, which was followed by 5 mg decrease every 2 weeks until the treatment was discontinued. No signs of recurrence have since been identified.

**Discussion**

PG is a rare inflammatory disease of the skin that is often associated with systemic inflammatory disorders such as IBD. For prompt diagnosis, PG should be considered in IBD patients when the characteristic ulcerative lesions of the skin are diffusely seen in any part of the body. Antibiotic resistance may help suggest a diagnosis of PG. Once suspected,
consultation with a dermatology clinic for skin biopsy is needed to confirm the diagnosis. In our case, bacterial cellulitis was initially suspected, but the diagnosis of PG was made based on pathological examination of the skin biopsy.

GMA is a therapeutic strategy of extracorporeal immunomodulation that effectively removes activated leukocytes, particularly activated granulocytes and macrophages, from peripheral blood to correct imbalances in immunological regulatory mechanisms (12). Since the activation of granulocytes has been suggested to play an important role in the pathogenesis of PG (5), we selected GMA as a treatment option for the patient of the present case. This technique was initially introduced for the treatment of UC as a once-weekly regimen (12), and a recent study showed that a twice-weekly regimen (intensive GMA) could achieve significantly higher ratios of clinical remission and mucosal healing compared with the original format (13).

To date, 15 cases of PG treated with leukocytapheresis (including the present case) have been reported (8, 14-20) (Table 2). The efficacy of a twice-weekly regimen has not been confirmed for skin diseases, including PG (17), although the efficacy of the standard GMA regimen has been

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**Table 2.** Previously Reported Cases of PG Treated with Apheresis Therapy.

<table>
<thead>
<tr>
<th>Sex/Age</th>
<th>Type of apheresis</th>
<th>Number of session</th>
<th>Regimen</th>
<th>Associated disease</th>
<th>Treatment before apheresis</th>
<th>Efficacy</th>
<th>Reference</th>
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<tbody>
<tr>
<td>M/19</td>
<td>GMA</td>
<td>10</td>
<td>Standard CD</td>
<td>5-ASA</td>
<td>Excellent</td>
<td>(14)</td>
<td></td>
</tr>
<tr>
<td>F/60</td>
<td>GMA</td>
<td>5</td>
<td>Standard RA</td>
<td>GC</td>
<td>Excellent</td>
<td>(15)</td>
<td></td>
</tr>
<tr>
<td>M/67</td>
<td>GMA</td>
<td>5</td>
<td>Standard RA</td>
<td>GC</td>
<td>Excellent</td>
<td>(15)</td>
<td></td>
</tr>
<tr>
<td>F/64</td>
<td>GMA</td>
<td>5</td>
<td>Standard RA</td>
<td>GC</td>
<td>Excellent</td>
<td>(15)</td>
<td></td>
</tr>
<tr>
<td>M/42</td>
<td>LCAP</td>
<td>5</td>
<td>Standard UC</td>
<td>GC, SASP</td>
<td>Excellent</td>
<td>(16)</td>
<td></td>
</tr>
<tr>
<td>M/67</td>
<td>GMA</td>
<td>10</td>
<td>* none</td>
<td>GC, CsA</td>
<td>Excellent</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>M/44</td>
<td>GMA</td>
<td>8</td>
<td>* none</td>
<td>GC, DDS</td>
<td>Good</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>M/38</td>
<td>GMA</td>
<td>4</td>
<td>Standard none</td>
<td>GC, DDS</td>
<td>Excellent</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>M/40</td>
<td>GMA</td>
<td>10</td>
<td>Intensive none</td>
<td>GC, DDS, CsA, AZA, CPA</td>
<td>Excellent</td>
<td>(18)</td>
<td></td>
</tr>
<tr>
<td>F/43</td>
<td>GMA</td>
<td>10</td>
<td>Standard none</td>
<td>GC, CsA, SASP</td>
<td>Excellent</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>F/29</td>
<td>GMA</td>
<td>10</td>
<td>Standard UC</td>
<td>GC, SASP</td>
<td>Excellent</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>M/65</td>
<td>GMA</td>
<td>11</td>
<td>Standard RA</td>
<td>GC, CPA, DDS, CsA</td>
<td>Good</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>F/60</td>
<td>LCAP</td>
<td>4</td>
<td>Standard UC</td>
<td>GC, DDS, CsA</td>
<td>Excellent</td>
<td>(19)</td>
<td></td>
</tr>
<tr>
<td>F/73</td>
<td>LCAP</td>
<td>10</td>
<td>Standard IBD</td>
<td>GC, DDS, CsA</td>
<td>Good</td>
<td>(20)</td>
<td></td>
</tr>
<tr>
<td>F/36</td>
<td>GMA</td>
<td>10</td>
<td>Intensive UC</td>
<td>SASP</td>
<td>Excellent [present case]</td>
<td></td>
<td></td>
</tr>
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established in patients with corticosteroid- and immunosuppressant-resistant PG (11, 18). For the present case, we applied an intensive GMA regimen with corticosteroids in the expectation of a rapid improvement of severe skin and colonic mucosal lesions. The effect of the intensive GMA regimen itself was unclear in this case, because GMA and corticosteroid therapy were started simultaneously. However, the rapid improvement of the skin and colonic mucosal lesions after 3 GMA sessions, as well as the favorable corticosteroid reduction, potentially suggests the effects of the intensive GMA regimen. Further studies evaluating the clinical utility of intensive GMA regimens against skin diseases should be undertaken in the future.

The clinical challenge of PG associated with IBD is the selection of the appropriate treatment. The management of PG is mainly based on clinical experience. No standard therapeutic approach for the improvement of both skin and intestinal lesions has been established. For patients with PG associated with IBD, systemic corticosteroids have been recommended as the first-line therapy with or without immunomodulators (azathioprine or 6-mercaptopurine), although the evidence supporting their use is weak (21). Definitive healing rates with oral corticosteroids have been reported to be less than 30% in PG with IBD patients (22). As other options, intravenous cyclosporine and tacrolimus may be considered for cases that are refractory to corticosteroid therapy (23). Anti-tumor necrosis factor (TNF) agents such as infliximab may also be useful as a new treatment option. The efficacy of infliximab was confirmed in a multicenter clinical trial of PG cases treated with infliximab or a placebo, including 19 patients with IBD (24, 25). However, these medications (corticosteroids, cyclosporine, tacrolimus and anti-TNF drugs) are all associated with the increased risk of opportunistic infection (26). Moreover, when used in combination, these drugs synergistically increased the likelihood of opportunistic infection (26). In contrast, no reports have described opportunistic infection occurring in association with GMA treatment. The excellent safety profile of GMA has been confirmed in numerous studies (9, 27, 28), and makes GMA an attractive option for patients who are refractory to conventional therapy.

Since randomized prospective trials have not been performed, the standard therapeutic strategy PG and UC has not been established. We emphasize that an intensive regimen of GMA may offer an ideal option for patients with severe and refractory PG complicated with UC.

Author's disclosure of potential Conflicts of Interest (COI).
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References


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