

World Journal of *Clinical Cases*

World J Clin Cases 2020 June 6; 8(11): 2066-2407



**REVIEW**

- 2066** Tumor circulome in the liquid biopsies for digestive tract cancer diagnosis and prognosis
Chen L, Chen Y, Feng YL, Zhu Y, Wang LQ, Hu S, Cheng P
- 2081** Isoflavones and inflammatory bowel disease
Wu ZY, Sang LX, Chang B

MINIREVIEWS

- 2092** Cytapheresis for pyoderma gangrenosum associated with inflammatory bowel disease: A review of current status
Tominaga K, Kamimura K, Sato H, Ko M, Kawata Y, Mizusawa T, Yokoyama J, Terai S
- 2102** Altered physiology of mesenchymal stem cells in the pathogenesis of adolescent idiopathic scoliosis
Ko DS, Kim YH, Goh TS, Lee JS
- 2111** Association between liver targeted antiviral therapy in colorectal cancer and survival benefits: An appraisal
Wang Q, Yu CR
- 2116** Peroral endoscopic myotomy for management of gastrointestinal motility disorder
Feng Z, Liu ZM, Yuan XL, Ye LS, Wu CC, Tan QH, Hu B

ORIGINAL ARTICLE**Case Control Study**

- 2127** Clinical prediction of complicated appendicitis: A case-control study utilizing logistic regression
Sasaki Y, Komatsu F, Kashima N, Suzuki T, Takemoto I, Kijima S, Maeda T, Miyazaki T, Honda Y, Zai H, Shimada N, Funahashi K, Urita Y
- 2137** Clinical application of ultrasound-guided selective proximal and distal brachial plexus block in rapid rehabilitation surgery for hand trauma
Zhang J, Li M, Jia HB, Zhang L
- 2144** High flux hemodialysis in elderly patients with chronic kidney failure
Xue HY, Duan B, Li ZJ, Du P
- 2150** Determination of vitamin D and analysis of risk factors for osteoporosis in patients with chronic pain
Duan BL, Mao YR, Xue LQ, Yu QY, Liu MY

Retrospective Study

- 2162** Differences in parents of pediatric liver transplantation and chronic liver disease patients
Akbulut S, Gunes G, Saritas H, Aslan B, Karipkiz Y, Demyati K, Gungor S, Yilmaz S
- 2173** Epidemiological investigation of *Helicobacter pylori* infection in elderly people in Beijing
Zhu HM, Li BY, Tang Z, She J, Liang XY, Dong LK, Zhang M
- 2181** Application of a pre-filled tissue expander for preventing soft tissue incarceration during tibial distraction osteogenesis
Chen H, Teng X, Hu XH, Cheng L, Du WL, Shen YM
- 2190** Evaluation of clinical significance of claudin 7 and construction of prognostic grading system for stage II colorectal cancer
Quan JC, Peng J, Guan X, Liu Z, Jiang Z, Chen HP, Zhuang M, Wang S, Sun P, Wang HY, Zou SM, Wang XS
- 2201** Choice and management of negative pressure drainage in anterior cervical surgery
Su QH, Zhu K, Li YC, Chen T, Zhang Y, Tan J, Guo S
- 2210** Risk scores, prevention, and treatment of maternal venous thromboembolism
Zhang W, Shen J, Sun JL
- 2219** Role of Hiraoka's transurethral detachment of the prostate combined with biopsy of the peripheral zone during the same session in patients with repeated negative biopsies in the diagnosis of prostate cancer
Pan CY, Wu B, Yao ZC, Zhu XQ, Jiang YZ, Bai S
- 2227** Efficacy of thoracoscopic anatomical segmentectomy for small pulmonary nodules
Li H, Liu Y, Ling BC, Hu B

Observational Study

- 2235** Attitudes, awareness, and knowledge levels of the Turkish adult population toward organ donation: Study of a nationwide survey
Akbulut S, Ozer A, Gokce A, Demyati K, Saritas H, Yilmaz S
- 2246** Metabolic biomarkers and long-term blood pressure variability in military young male adults
Lin YK, Liu PY, Fan CH, Tsai KZ, Lin YP, Lee JM, Lee JT, Lin GM
- 2255** Cytokines predict virological response in chronic hepatitis B patients receiving peginterferon alfa-2a therapy
Fu WK, Cao J, Mi NN, Huang CF, Gao L, Zhang JD, Yue P, Bai B, Lin YY, Meng WB

SYSTEMATIC REVIEWS

- 2266** Utilising digital health to improve medication-related quality of care for hypertensive patients: An integrative literature review
Wechkunanukul K, Parajuli DR, Hamiduzzaman M

META-ANALYSIS

- 2280** Role of *IL-17* gene polymorphisms in osteoarthritis: A meta-analysis based on observational studies
Yang HY, Liu YZ, Zhou XD, Huang Y, Xu NW

CASE REPORT

- 2294** Various diagnostic possibilities for zygomatic arch pain: Seven case reports and review of literature
Park S, Park JW
- 2305** Extensive multifocal and pleomorphic pulmonary lesions in Waldenström macroglobulinemia: A case report
Zhao DF, Ning HY, Cen J, Liu Y, Qian LR, Han ZH, Shen JL
- 2312** Lung cancer from a focal bulla into thin-walled adenocarcinoma with ground glass opacity – an observation for more than 10 years: A case report
Meng SS, Wang SD, Zhang YY, Wang J
- 2318** Pyogenic discitis with an epidural abscess after cervical analgesic discography: A case report
Wu B, He X, Peng BG
- 2325** Clinical characteristics, diagnosis, and treatment of COVID-19: A case report
He YF, Lian SJ, Dong YC
- 2332** Paraplegia after transcatheter artery chemoembolization in a child with clear cell sarcoma of the kidney: A case report
Cai JB, He M, Wang FL, Xiong JN, Mao JQ, Guan ZH, Li LJ, Wang JH
- 2339** Macrophage activation syndrome as a complication of dermatomyositis: A case report
Zhu DX, Qiao JJ, Fang H
- 2345** Serial computed tomographic findings and specific clinical features of pediatric COVID-19 pneumonia: A case report
Chen X, Zou XJ, Xu Z
- 2350** Myxofibrosarcoma of the scalp with difficult preoperative diagnosis: A case report and review of the literature
Ke XT, Yu XF, Liu JY, Huang F, Chen MG, Lai QQ
- 2359** Endoscopic pedicle flap grafting in the treatment of esophageal fistulas: A case report
Zhang YH, Du J, Li CH, Hu B
- 2364** Hemophagocytic syndrome as a complication of acute pancreatitis: A case report
Han CQ, Xie XR, Zhang Q, Ding Z, Hou XH
- 2374** Reduced delay in diagnosis of odontogenic keratocysts with malignant transformation: A case report
Luo XJ, Cheng ML, Huang CM, Zhao XP

- 2380** Gastric pyloric gland adenoma resembling a submucosal tumor: A case report
Min CC, Wu J, Hou F, Mao T, Li XY, Ding XL, Liu H
- 2387** Ataxia-telangiectasia complicated with Hodgkin's lymphoma: A case report
Li XL, Wang YL
- 2392** Uterine incision dehiscence 3 mo after cesarean section causing massive bleeding: A case report
Zhang Y, Ma NY, Pang XA
- 2399** Optical coherence tomography guided treatment avoids stenting in an antiphospholipid syndrome patient: A case report
Du BB, Wang XT, Tong YL, Liu K, Li PP, Li XD, Yang P, Wang Y

LETTER TO THE EDITOR

- 2406** Macrophage activation syndrome as an initial presentation of systemic lupus erythematosus
Shi LJ, Guo Q, Li SG

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Cytapheresis for pyoderma gangrenosum associated with inflammatory bowel disease: A review of current status

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Abstract

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis clinically characterized by the presence of painful skin ulcerations with erythematous. As it is frequently associated with inflammatory bowel diseases, including ulcerative colitis, gastroenterologists should be familiar with the disease including therapeutic options. Therefore, we have conducted a review focusing on the cytapheresis for PG in cases of inflammatory bowel diseases. A literature search was conducted to extract studies published in the last 20 years, with information on demographics, clinical symptoms, treatment, and the clinical course from a total of 22 cases reported and our recent case. In most patients, cytapheresis was associated with improvement or resolution of PG after failure of conventional therapeutic options such as corticosteroids, antibiotics, immunosuppressive agents and immunoglobulin. Based on the information summarized, cytapheresis is helpful in the majority of patients with PG refractory to medical treatment associated with inflammatory bowel diseases and could be further studied in a multicenter, randomized trial.

Key words: Granulocytapheresis; Leucocytapheresis; Cytapheresis; Inflammatory bowel diseases; Pyoderma gangrenosum; Complications

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Core tip: Pyoderma gangrenosum is one of the neutrophilic dermatoses often complicated with ulcerative colitis. The corticosteroid and other immune modulator have been used for the treatment, however, as its disease mechanism has not been clarified, there is no additional option for those who showed poor response and refractory to the conventional therapies. Based on the recent reports, we have summarized the clinical course of 23 cases and efficacy of cytapheresis. Although well-designed prospective clinical trials are essential to develop the evidences, however, the information could help physicians in the

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gastroenterology field to understand the disease and therapeutic options.

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INTRODUCTION

Pyoderma gangrenosum (PG), an inflammatory disease, is one of the neutrophilic dermatoses^[1]. It is clinically characterized by painful skin ulcerations with erythematous and undermined borders, and histologically by the presence of neutrophilic infiltrates in the dermis^[1,2]. It can present in several variants to a variety of health professionals and may not always be easily recognized. The annual incidence of PG is estimated at 3-10 per million persons^[1], and is mostly associated with ulcerative colitis (UC) and Crohn's disease. Other association include rheumatoid arthritis (RA), seronegative arthritis, myelodysplastic syndrome, multiple myeloma, polycythemia vera, paraproteinemia, and leukemia^[2].

Treatment of PG usually may include high-dose glucocorticoids (GC), dapsone, minocycline, methotrexate (MTX), cyclosporine (CsA), mycophenolate mofetil, intravenous immunoglobulin, tumor necrosis factor (TNF)-alpha inhibitors, and surgical options, usually colectomy^[2,3]. Alternatively, granulocytapheresis (GCAP)/granulocyte and monocyte apheresis (GMA), and leucocytapheresis (LCAP) are therapeutic strategies of extracorporeal immunomodulation that can selectively remove activated leukocytes from the peripheral blood^[4-6]. Kanekura *et al*^[7] reported the efficacy of GCAP/GMA for the first time in 2002 and this was supported by a report of LCAP in PG in 2003^[8]. In 2017, Russo *et al*^[9] firstly reported the efficacy of GCAP/GMA on PG other than the reports from Japan. For evaluating the efficacy of cytapheresis in PG treatment, we performed a literature review including all the case reports of PG associated with inflammatory bowel diseases (IBD) treated by cytapheresis, since 2002. We believe that the information summarized in this mini-review will help the management of patients with PG and perhaps result in more formal trials of this novel therapy.

LITERATURE ANALYSIS

A literature search was conducted using PubMed, Ovid, and Ichushi provided by the Japan Medical Abstract Society, with the terms "cytapheresis", "GMA", "GCAP", or "LCAP," and "pyoderma gangrenosum" to extract the studies published in the last 20 years. The studies written in English and Japanese from relevant publications were selected. We have summarized the information on demographics, clinical symptoms, treatments, and the clinical courses from articles, including 22 case reports in Tables 1 and 2.

EPIDEMIOLOGY

The annual incidence of PG is estimated to be approximately 3-10 patients per million persons and it usually affects patients of ages 20-50 years, and females more commonly than males. Infants and adolescents account for only 4% of the cases^[10]. The etiology and mechanisms causing PG is unknown; however, 50%-70% of cases are associated with other diseases, such as IBD, arthritis, and lymphoproliferative disorders. PG is believed to involve abnormal immune responses and, possibly, vasculitis^[11]. IBD is the most common comorbidity in PG, and PG constitutes approximately 1%-3% of the extraintestinal manifestations in patients with IBD^[12,13]. To verify the effect of cytapheresis on PG in IBD patients treated with GCAP/GMA, and LCAP^[7-9,14-37] especially with IBD, we summarized 22 reported cases^[8,14-17,20-29,31-37] and our case of PG (Table 1). the average age was 39.6 years (range, 19-73) and the ratio of males to females was 8:15 (Table 1) similar to the previous reports^[1].

Table 1 Clinical characteristics of cases treated with cytapheresis

Case (number)	Ref.	First authors	Reporting year	Age (yr)	Gender	The site of PG	Associated disease	Treatment before apheresis
1	[8]	Ohmori T	2003	19	M	Buttocks and legs	CD	5-ASA
2	[14]	Ishikawa H	2004	30	M	Abdomen, right iliac	UC	GC, CsA
3	[15]	Murata M	2004	31	M	Right lower leg	UC	GC
4	[16]	Yoneda K	2005	39	F	Face and head	UC	GC
5	[17]	Yanar-Fujisawa R	2005	31	F	Left ankle and right knee	UC	GC
6	[20]	Seishima M	2007	29	F	Lower bilateral legs	UC	GC, SASP
7	[21]	Fujino Y	2008	55	F	Lower bilateral legs	UC	GC, 5-ASA
8	[22]	Kawakami T	2009	19	M	Head	UC	GC, SASP
9	[23]	Doi R	2010	19	M	Forehead	UC	GC, SASP
10	[24]	Kobayashi S	2011	29	M	Right lower leg	UC	GC, SASP
11	[25]	Ikeda K	2011	36	F	Lower leg, neck and upper trunk	UC	GC
12	[26]	Uchiyama K	2011	50	F	Lower limbs	UC	GC
13	[27]	Urushibara M	2014	44	F	Back, left leg	UC	GC, 5-ASA, FK506
14	[28]	Izaki S	2014	49	F	Forearms	UC	SASP, PI
15	[29]	Ohno M	2016	36	F	Lower limbs	UC	SASP
16	[31]	Okada M	2017	71	F	Buttocks	UC	GC, 5-ASA
17	[32]	Yamashita A	2017	30	F	Top of the foot	UC	5-ASA
18	NA	Our Case	2018	57	M	Left lower leg	UC	GC, 5-ASA
19	[33]	Murata M	2003	19	F	Lower left leg	UC	GC
20	[34]	Fujimoto E	2004	42	M	Legs	UC	GC, SASP
21	[35]	Watanabe Y	2008	60	F	Left dorsal femur	UC	GC, DDS, CsA
22	[36]	Hanafusa T	2011	73	F	Sternum and chest	IBD, breast cancer	GC, DDS, CsA
23	[37]	Ito A	2015	43	F	Lower left leg	UC	GC, SASP

M: Male; F: Female; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; RA: rheumatoid arthritis; MDS: Myelodysplastic syndromes; GC: Glucocorticoid; SASP: Salazosulfapyridine; 5-ASA: 5-aminosalicylic acid; CsA: Cyclosporine; PI, potassium iodide; DDS: Diamino diphenyl sulfone; NA: Not available.

CLINICAL COURSE

Symptoms

The clinical course is unpredictable; it may not correlate with IBD activity and may even precede a diagnosis of IBD. PG most commonly affects the lower legs; however, PG at other sites of the body have been reported as well, including the breast, hand, trunk, head and neck, and peristomal skin. Overall, 25% of patients with PG have confirmed lesions on the head and neck^[38,39]. We found that the clinical symptoms of PG were seen in all 23 cases and included the following distribution of the skin lesions: most of cases showed PG in lower limbs, followed by upper limbs, trunk, head and neck, buttocks, and site of postoperative wound (Table 1)^[8,14-17,20-29,31-37]. Lower limb lesions were the most common lesions in these patients. The size of the skin lesions varied from 4 cm × 2 cm to 11 cm × 12 cm in diameter. PG is a painful and unsightly dermatologic disorder with the potential to significantly decrease a patient's quality of life (QOL).

Treatments

A variety of drugs have been used to treat PG, including high-dose GC, dapsone, minocycline, MTX, CsA, mycophenolate mofetil, intravenous immunoglobulin, and

Table 2 Clinical course of the cases

Case (number)	Type of apheresis	Ulcer before the treatment	Number of therapies	CRP mg / dL (before, after)	WBC / μ L (before, after)	Neutrophils % (before, after)	Clinical courses	Side effect	Relapse (follow up)
1	GCAP	NA	10	19.9, 0.6	17900, 4700	NA	Ulcer was fully re-epithelialized after 10 weeks	NA	NA
2	GCAP	NA	5	2.91, negative	NA	NA	Complete healing after 5 th treatment	Mild headache	Yes (5 mo)
3	GCAP	NA	5	NA	NA	NA	Improve after 5 th treatment	NA	NA
4	GCAP	NA	NA	NA	NA	NA	Symptoms were relieved with frequent GCAP and granulocyte-penic therapy	NA	-
5	GCAP	NA	5	NA	NA	NA	Complete healing after 5 th treatment	NA	-
6	GCAP	9 cm	10	NA	NA	NA	Pain relieved 2 nd treatment; ulcers were re-epithelialized after 4 th treatment	None	-
7	GCAP	NA	10	7.1, negative	NA	NA	Ulcer was fully re-epithelialized after 9 th treatment	NA	-
8	GCAP	NA	NA	NA	NA	NA	Complete healing after the treatment	NA	-
9	GCAP	NA	11	NA	NA	NA	Ulcer was fully re-epithelialized one month after the 1 st treatment	NA	-
10	GCAP	NA	5	NA	NA	NA	Ulcer improved partly but remained	NA	Yes (2 mo)
11	GCAP	7 cm	5	13.71, 0.21	NA	NA	Ulcer improved after 5 th treatment	None	No (6 mo)
12	GCAP	6.5 cm	10	NA	NA	NA	Ulcer was fully re-epithelialized 3 month after the 10 th treatment	NA	Yes (6 mo)
13	GCAP	NA	10	12.1, negative	NA	NA	Ulcer was fully re-epithelialized after the 10 th treatment	NA	-
14	GCAP	NA	5	NA	NA	NA	Ulcer improved 2 months after the 5 th treatment	NA	2 times (1 mo, 2 mo)

15	GCAP	NA	10	6.53, negative	NA	NA	Ulcer and symptoms improved after 3 rd treatment	None	-
16	GCAP	3.1 cm	10	NA	NA	NA	Ulcer was fully re-epithelialized 2 months after the 1 st treatment	None	No (2 yr)
17	GCAP	NA	10	4.73, negative	NA	NA	Ulcer was fully re-epithelialized after the 10 th treatment	NA	-
18	GCAP	7 cm	10	0.45, 0.04	12310, 7490	74.9, 89.0	Ulcer was partly re-epithelialized after the 10 th treatment	None	No (4 yr)
19	LCAP	NA	5	7.76, negative	NA	NA	Ulcer was partly re-epithelialized after the 3 rd treatment	NA	-
20	LCAP	NA	5	1.3, 0.3	10400, 6400	88, 60	Ulcer was fully re-epithelialized after the 3 rd treatment	None	No (4 mo)
21	LCAP	4 cm	4	6.6, 0.1	10800, 9100	84, 90	Skin lesion improved 3 months after the 4 th treatment	NA	-
22	LCAP	7 cm	10	4.7, 1.3	11900, 7140	NA	Ulcer was fully re-epithelialized after the first round of LCAP, recurred with the tapering of PSL during the 2 nd period of LCAP.	NA	No (2 yr)
23	LCAP	NA	10	22.46, negative	NA	NA	Ulcer and symptoms improved after 10 th treatment	NA	No

GCAP: Granulocytapheresis; LCAP: Leukocytapheresis; CRP: C-reactive protein; WBC: White blood cell; NA: Data not available

TNF-alpha inhibitors^[2,3]. The first-line of treatment for PG includes oral corticosteroids. In patients who do not respond, TNF-alpha inhibitors constitute the second-line of treatment^[40]. Cytapheresis (GCAP/GMA and LCAP) has also been reported to be effective in PG for those cases refracted to GC. However, due to the small number of patients treated with cytapheresis and the unknown etiology, there is no established protocol of cytapheresis for PG. The clinical courses of case reports have been summarized in Table 2. Among the 23 cases, GC was used for 19 cases, CsA for 4 cases, diamino diphenyl sulfone for 1 case, salazosulfapyridine for 8 cases, 5-aminosalicylic acid for 6 cases, MTX for 2 cases, cyclophosphamide for 1 case, potassium iodide (PI) in 2 cases, and FK506 in 1 case, however, none of these 23 cases showed therapeutic effect on the ulcers^[8,14-17,20-29,31-37].

CYTOPHERESIS

The 23 cases of cytapheresis included 18 cases of GCAP/GMA and 5 cases of LCAP

(Tables 1 and 2)^[8,14-17,20-29,31-37].

GCAP/GMA

GCAP/GMA is an extracorporeal apheresis technique in which a specialized column (Adacolumn, Japan Immunoresearch Laboratories, Takasaki, Japan) selectively traps activated granulocytes and monocytes/macrophages from the peripheral blood^[41]. It was initially approved for the treatment of UC because it traps activated granulocytes^[42,43]. Furthermore, it has been used in the treatment of several inflammatory diseases because neutrophils are crucial in their pathogenesis. A recent report demonstrated that the serum levels of inflammatory cytokines such as interleukin (IL)-1 β , IL-6, IL-8, and TNF-alpha were markedly reduced by GCAP/GMA along with downregulation of L-selectin and the chemokine receptor CXCR3^[41]. GCAP/GMA has also been reported to be effective in other disorders that are attributable to activated neutrophils, including PG. To prove this phenomenon, clinical trials of GCAP/GMA in the treatment of various skin diseases such as psoriasis, RA, systemic lupus erythematosus (SLE), Sweet's disease, and PG are underway^[18]. The effect of the treatment was various in each case and the change of serum CRP levels between pre- and post-treatment was investigated (Table 2). There were no reports of major side effects; headache was reported as a side effect in only one case. In 4 of 23 cases (17%), recurrence was observed and in three of those cases, complete cure was not achieved during the recurrence. The reasons for the recurrence may involve the discontinuation of treatment before the confirmation of the complete healing of the ulcer.

LCAP

LCAP is performed using a column designed to remove leukocyte contributing the inflammation, which is related to the activity of PG and UC^[6]. The column is an extracorporeal perfusion type white blood cell apheresis unit. The column, Cellsorba (Asahi Kasei Medical, Tokyo, Japan), is composed of a filter within a filter, each composed of non-woven polyethylene terephthalate fabric, with both filters wound into a cylindrical shape and sealed with polyurethane. There were no reported adverse effects of LCAP, such as nausea, vomiting, and liver dysfunction, or recurrence of the lesions during the therapy^[37]. The removal rate of activated granulocytes is 2-3 times that with GCAP/GMA. Furthermore, LCAP also has the ability to remove activated platelets, which irritate the granulocytes and release reactivated oxygen species^[4]. We believe that LCAP may be a valuable tool in treating intractable PG in patients without lymphocytopenia and thrombocytopenia, however, due to the shortage of materials, it will not be able to be performed in Japan soon.

DISCUSSION

In terms of efficacy of cytapheresis, both GCAP/GMA and LCAP were effective treating PG that was resistant to steroids and other treatments. The ulcers of the lower extremities in PG result in gait disorders and significantly reduce QOL. In some cases, improvements in QOL have been reported following cytapheresis^[24,26]. The frequency of LCAP in treating PG is less than that required with GCAP/GMA. Furthermore, the recurrence rate in LCAP is lower than that in GCAP/GMA. There were no reports of adverse side effects in both therapies; however, the number of cases is still small and further evaluations are necessary. The methods, advantages, and disadvantages of both GCAP/GMA and LCAP have been summarized in Table 3^[4-6,37]. Both, GCAP/GMA and LCAP have a direct immunosuppressive effect by removing the activated leukocytes involved in the pathogenesis, an indirect anti-inflammatory action via complement activity, and result in functional improvements of regulatory T-cells. The main difference, however, is that LCAP has a high removal rate of not only granulocytes but also lymphocytes and activated platelets (Table 3). There were 4 cases of recurrences following several months after GCAP/GMA therapy^[14,24,26,28]. On the other hand, LCAP was effective in all cases and there was no case of recurrence. Therefore, the therapeutic effect of LCAP in PG is presumed to be better. LCAP is considered to be more effective because the inflamed mucous membranes in UC with a long duration of illness are mainly elicited by the lymphocytes. Additionally, in cases of UC with deep and widespread ulcers, it has been reported that active platelets occlude and inhibit tissue regeneration^[44]. Furthermore, in the peripheral blood of patients with RA and UC, microparticles derived from activated platelets increase and indirectly induce the release of chemokines and cytokines, which are important factors that cause thrombosis and inflammation^[45]. By removing these platelets and microparticles, LCAP can prevent microvascular occlusion, promote tissue regeneration and epithelialization, and suppress cytokine-related

inflammation^[46]. Although the mechanism of cytapheresis in the treatment of PG is unknown, it has recently been reported that both neutrophils, on whose surface adhesion molecules such as Mac-1^[19] and intercellular adhesion molecule-1 are expressed^[47], and circulating levels of inflammatory cytokines such as IL-8 and granulocyte colony stimulating-factor decrease following GCAP/GMA therapy. Recently, Nomura *et al*^[48] demonstrated in their retrospective study that cytapheresis was effective not only for inducing remission for UC itself but also for extra-intestinal dermal lesions of PG and erythema nodosum suggesting the efficacy of cytapheresis therapy for UC. The development of biologics for IBD will contribute to improve the various symptoms including PG, and therefore the further assessment and the accumulation of the cases are essential.

CONCLUSION

In conclusion, for the cases of PG showing resistance to GC or other conventional therapies, cytapheresis with either GCAP/GMA or LCAP has the potential to be an effective and safe therapeutic option. It is clear; however, additional cases, information, and well-designed prospective clinical trials are necessary to develop the evidences to be one of the standardized therapies. From this point, our mini-review summarizing the cases of PG treated with cytapheresis will help physicians to understand the cytapheresis and treat cases with PG.

Table 3 Summary of cytapheresis

Treatment	Adsorbent	Blood volume	Common mechanism	Advantages/features	Diseases	Contraindications	Major adverse events reported
GCAP/GMA	Cellulose acetate	1.5-2.0 L	Mobilization of naive leukocytes by activated leukocyte removal; Inhibition of Cellular Invasion of Activated Leukocytes; Suppression of inflammatory cytokines, increase of anti-inflammatory cytokines	High specificity for removing WBCs. 30%-50% removal of granulocytes and monocytes, and approximately 6% removal of lymphocytes	Ulcerative colitis; Crohn's disease; Pustular psoriasis; Pyoderma Gangrenosum	Granulocyte < 2000/mm ³ associated with infection	Allergic symptoms; Nausea; Fever; Abdominal oppression; Headache
LCAP	Polyethylene-telephthalate	2.0-4.0 L		High efficiency for removing WBCs Almost all granulocytes and monocytes, and 40%-60% of lymphocytes and platelets can be removed Increase of naive T cells can be seen and its therapeutic effect can be expected by suppressing antibody production and immune reaction	Ulcerative colitis; Rheumatoid arthritis	Treatment with angiotensin-converting enzyme inhibitors	

GCAP: Granulocytapheresis; LCAP: Leukocytapheresis; WBC: White blood cell.

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