Renal Replacement Therapy

CASE REPORT

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A case of severe generalized pustular psoriasis successfully treated with IL-17A monoclonal antibody and granulocyte removal therapy

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Abstract

Background: Generalized pustular psoriasis (GPP) usually presents with fever, generalized flushing, and multiple sterile pustules on the skin, which histopathologically form subcorneal pustules characterized by Kogoj spongiform pustules. Granulocyte/monocyte adsorption apheresis (GMA) was approved in Japan in 2012. The use of biologics for psoriasis treatment is increasing. Several case reports have evaluated the combination of GMA and cyclosporine (CyA) for GPP. However, very few English reports on combining biologics and GMA in treating GPP exist.

Case presentation: A 79-year-old man with a history of hypertension, diabetes mellitus, chronic kidney disease, and atrial fibrillation was admitted. He had been consulting a dermatologist for psoriasis vulgaris (PV) since the age of 44. The patient was diagnosed with severe GPP and treated with 300 mg secukinumab (SEC) on day 3. SEC is a fully human monoclonal IgG1 antibody that targets IL-17A. Five doses were administered. In addition, GMA was administered once a week, three times from day 4. After the first administration of GMA, the inflammatory response and skin condition improved markedly. The patient was discharged from the hospital on day 34.

Conclusions: The present study is the first English-written report on the combined administration of SEC and GMA both instituted since admission for severe GPP, with immediate patient response to treatment. Notably, IL-17A plays a vital role in the pathogenesis of GPP. GMA can eliminate activated leukocytes, and the early introduction of combined IL-17 monoclonal antibody and GMA may allow disease suppression in patients with severe GPP, thus avoiding progression to multiorgan failure. Further studies may verify the effects of IL-17 monoclonal antibodies and GMA on severe GPP.

Keywords: Generalized pustular psoriasis, Granulocyte and monocyte adsorption apheresis, Secukinumab

Background

Generalized pustular psoriasis (GPP) usually presents with fever, generalized flushing, and multiple sterile pustules on the skin, which histopathologically form subcorneal pustules characterized by Kogoj spongiform pustules. GPP may or may not be preceded by psoriatic eruption, and recurrence is characteristic of this disease.

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During the course of the disease, patients may exhibit abnormal laboratory findings associated with systemic inflammation and often show mucosal symptoms and arthritis complications; more rarely, respiratory insufficiency, ocular symptoms, and secondary amyloidosis are present. In 2012, granulocyte and monocyte adsorption apheresis (GMA) was approved in Japan to remove granulocytes and monocytes [1]. Here, we report a case of severe GPP where an early combination of anti-IL-17 monoclonal antibody and GMA resulted in the safe induction of remission. The use of biologics for the treatment of psoriasis is increasing. The administration of Infliximab (IFX) and secukinumab (SEC) for the treatment of GPP have insurance coverage in Japan.

Case presentation

A 79-year-old man with a history of hypertension, diabetes mellitus, chronic kidney disease, and atrial fibrillation was admitted to the hospital. This patient had had hypertension and diabetes since his 40 s. On admission, his blood pressure was 119/78 mmHg, under 25 mg losartan potassium. Despite his regular intake of 1 mg glimepiride, 20 mg teneligliptin, and 10 mg empagliflozin as an outpatient, his $HbA1_C$ was around 7.4–7.5%; thus, his diabetes was not well controlled. The patient's right kidney was virtually nonfunctional due to hydronephrosis and renal stones, and he had chronic kidney disease (CKD) G4 with eGFR 25.2 mL/min/1.73 m^2. Due to CKD progression, he had been switched to rivaroxaban 10 mg (from prior dabigatran 220 mg) for his atrial fibrillation three years earlier. On admission, his HR was about 110–120/min. He had a history of smoking 20 cigarettes per day until age 40. He had also maintained abstinence from alcohol since turning 40. This patient had been hospitalized 35 years before for a generalized skin rash and fever and attended our hospital for eight years for psoriasis vulgaris (PV). The skin rash appeared repeatedly, but it was an asteatotic eczema-like skin rash, which improved with topical betamethasone butyrate propionate ointment applied at weekends. One week before admission, the skin rash suddenly appeared on the upper body and showed a spreading tendency. Four days before admission, he was examined and found to have 37.7 °C body temperature and erythema with scaling on the trunk; thus, etretinate 30 mg was started on the same day. The skin rash became larger and larger, and his fever was above 38 °C.

He presented with diffuse erythema on the upper limbs, thighs, and trunk, as well as millet sized vesicles, which were scattered in clusters. The patient was admitted to the hospital as an emergency case on the same day. Laboratory data revealed an elevated inflammatory response (Table 1). One month before admission, his sCre was 2.01 mg/dL (eGFR 25.9 mL/min/1.73 m^2). On admission, his sCre was 2.43 mg/dL. Bearing in mind his pre-existing single-functioning kidney, the situation was consistent with acute kidney injury (AKI) on CKD. Based on the Japanese guidelines for the management and treatment of generalized pustular psoriasis [2], the patient was classified as severe (11–17), with a skin severity score of 8 (0–9) and a clinical and laboratory severity score of 7 (0–8) for a total score of 15 (Additional file 1: Figure S1). A skin biopsy was performed. Multiple pustule formations were observed in the epidermis with numerous neutrophilic clusters moving superiorly toward the stratum corneum with infiltrations between the surrounding spinous cells, as depicted in Fig. 1. In addition to the apparent pustules, the epidermis was infiltrated by neutrophils, mainly in the subcutaneous cornea, forming microabscesses. The patient was diagnosed with GPP; 300 mg of SEC was administered on day 3. A total of five doses were administered. In addition, from day 4, GMA was administered once a week for a period of three weeks (Fig. 2) using an Adacolumn device (JIMRO Co., Ltd, Takasaki, Japan). The duration of each GMA session was 60 min, and the flow rate was 30 ml/min. In addition, Nafamostat mesylate (30 mg/h) was administered as an anticoagulant. The inflammatory reaction and skin condition improved remarkably after the first GMA session, and the patient was discharged on day 34. Although the patient had severe extravascular leakage due to a cytokine storm, the early introduction of

Table 1 Blood data at admission, during antibody therapy, and before discharge

	Day 0	Day 7	Day 14	Reference range
White blood cell (/μl)	16,610	14,930	4930	3200–7900
Hemoglobin (g/dl)	14.4	11.3	10.4	11.3–15.0
Platelet ($\times 10^3$/μL)	15.1	15.9	20.2	155–350
Albumin (g/dL)	3.1	2.4	2.5	4.1–5.1
Blood urea nitrogen (mg/dL)	33.5	19.2	21.9	8–21
Serum Creatinine (mg/dL)	2.43	1.53	1.41	0.6–1.0
C-reactive protein (CRP)	31.8	19.3	3.3	< 0.3
Sodium (mEq/L)	133	139	142	138–145
Chloride (mEq/L)	96	107	110	101–108
Potassium (mEq/L)	4.2	3.9	4.5	3.6–4.8
Aspartate aminotransferase (IU/l)	22	38	32	11–38
Alanine transaminase (IU/l)	19	26	25	6–50
Lactate Dehydrogenase (IU/l)	182	112	117	103–190
Glucose (mg/dL)	157	166		73–109
Hemoglobin A1c (%)	7.1			4.9–6.0
Urine L-FABP (μg/gCre)	57.5			< 0.5

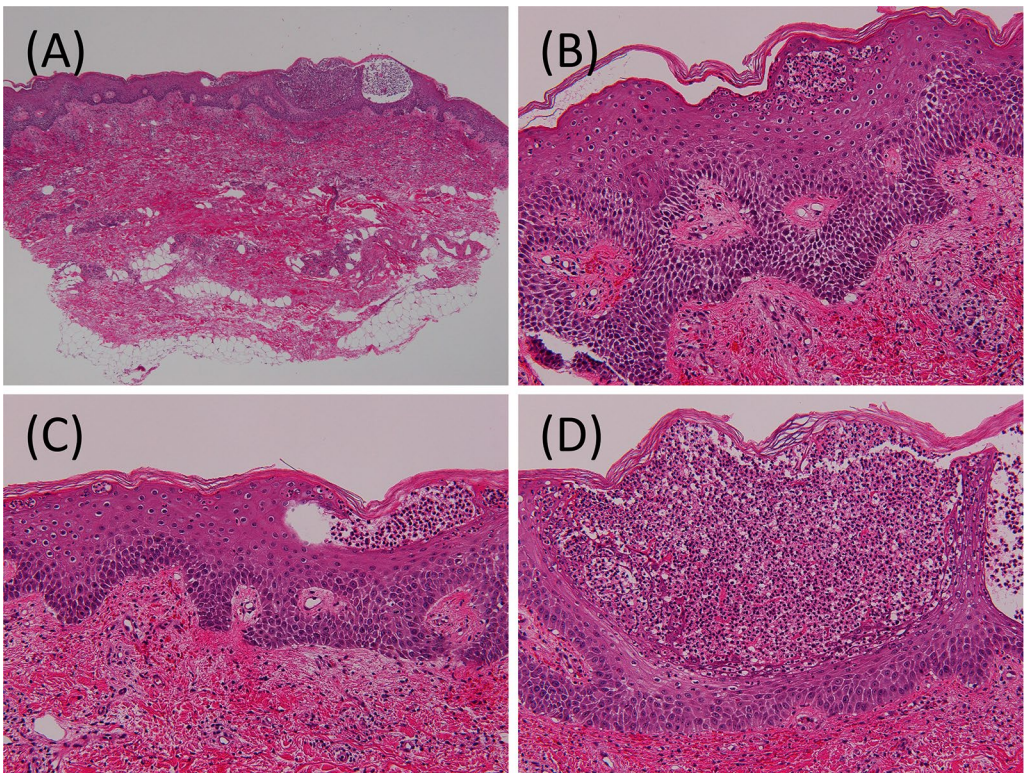

Fig. 1 Left thigh skin biopsy specimen. The sample was taken from the epidermis to the subcutaneous fatty tissue. Multiple pustule formations are seen in the epidermis with numerous neutrophilic clusters jumping up the stratum corneum, and infiltration is seen between the surrounding spinous cells. Other than the apparent pustules, the epidermis is also infiltrated by neutrophils, mainly in the subcutaneous cornea, often forming microabscesses. There is a mild extension of the epidermal processes on the basal side, which are relatively uniform in length. The dermis also shows inflammatory cell infiltrates, mainly lymphocytes, in shallow perivascular areas—findings of pustular psoriasis

IL-17 monoclonal antibodies and GMA successfully induced remission without progressing to multiple organ failure.

Discussion/conclusion

Biologics are becoming the mainstay of moderate-to-severe psoriasis treatment as they are effective, cause minor organ damage, and require fewer hospital visits than existing therapies. Currently, six drugs are used to treat psoriasis: IFX, adalimumab (ADA), ustekinumab (UST), SEC, ixekizumab (IXE), and brodalumab (BRO). The main types of psoriasis are psoriatic arthritis (PsA), GPP, and erythrodermic psoriasis (EP). In Japan, the treatment options for PV and PsA are IFX, ADA, UST, and SEC; treatment options for GPP are IFX and SEC; and treatment options for EP are IFX and SEC only. Cyclosporine (CyA) has a long history of use in dermatology, and its efficacy, dosage, and methods for managing its side effects are well established. However, since biologics are now available, concerns on the side effects of long-term administration of CyA, such as increased blood pressure and renal damage, exist. Several case reports evaluated the combination of GMA and CyA for GPP. However, there are very few English reports on the effectiveness of the combination of biologics and GMA for GPP. Fujisawa et al. reported the efficacy of IFX + GMA combination therapy in patients with GPP who failed to respond to IFX [3]. This is the first case study that reports on the combined administration of SEC and GMA both instituted since admission for severe GPP, with immediate patient response to treatment. Furthermore, when considering the pathogenesis of GPP, the suppression of IL-17A and removal of activated neutrophils are expected to be highly effective.

According to the 2003–2006 data retrieved from the Japanese Psoriasis Association, pustular psoriasis accounts for approximately 1% of all psoriasis cases, with the majority of patients being children and adults in their 30 s [2]. Men are twice as likely as women to be affected by PV, while pustular psoriasis is slightly more common in women (1.2 times more common than in men). The skin-related symptoms (erythema, pustules, edema) and findings associated with systemic inflammation (fever, white blood cell count, CRP level,

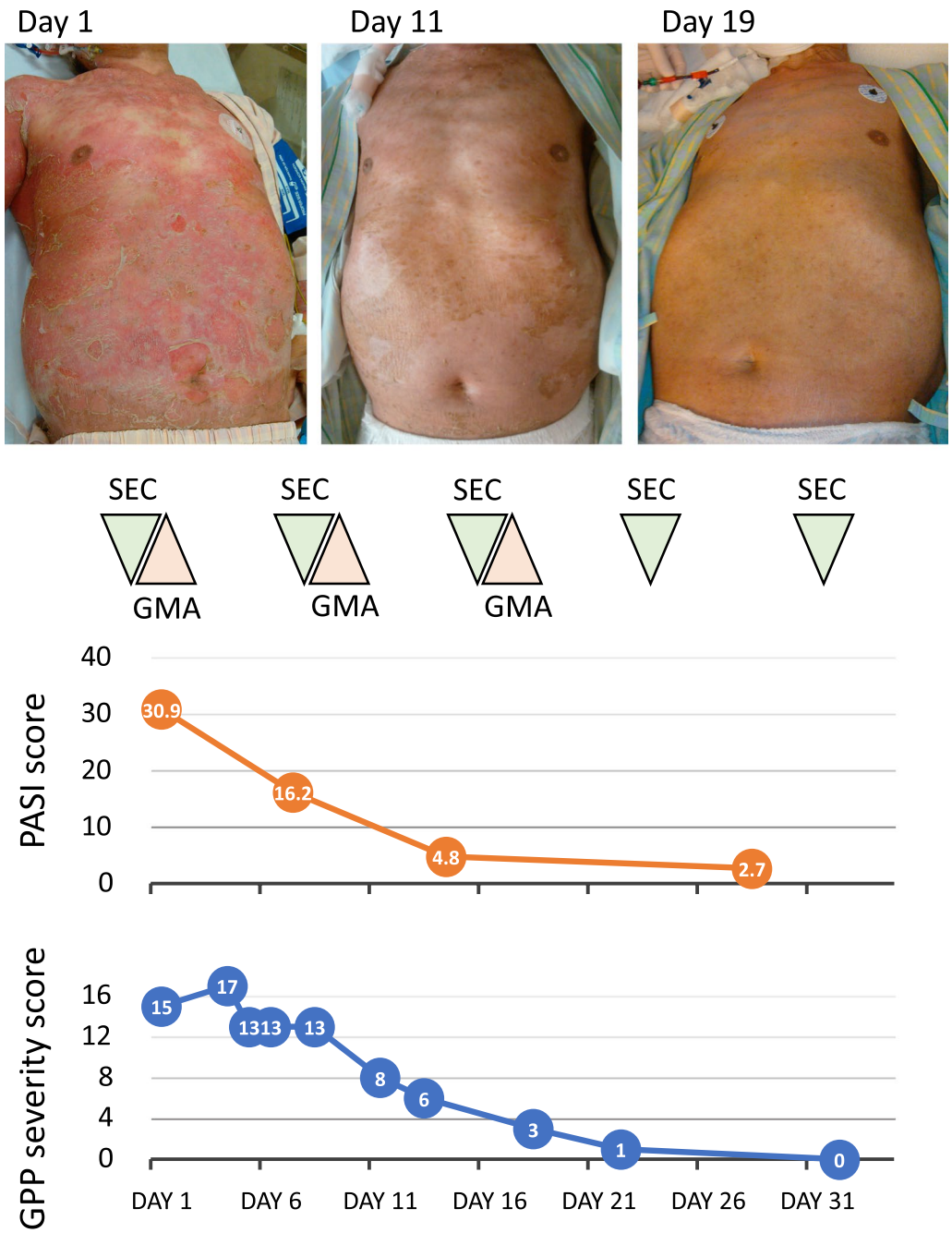

Fig. 2 The clinical course of the patient. The patient was diagnosed with severe GPP and was introduced to secukinumab (SEC) 300 mg on day 3. A total of five doses were administered. In addition, GMA was administered once a week, three times from day 4. After the first dose of GMA, inflammatory response improved markedly, and skin symptoms also improved. Psoriasis Area Sensitivity Index (PASI) scores also showed a decreasing trend after the start of treatment. The patient was discharged on the 34th sick day

and albumin level) were scored, and the total score was used to classify the disease as mild, moderate, or severe (Additional file 1: Figure S1). For the treatment of GPP, etretinate, cyclosporine, methotrexate, and corticosteroids are the drugs of choice, and topical medications, phototherapy, and GMA have been attempted. GPP is a disease that usually presents with fever, generalized flushing, and multiple aseptic pustules on the skin, which histopathologically appear as subcorneal leisons characterized by Kogoj spongiform pustules. PV

may or may not be preceded by a psoriatic eruption, but recurrent episodes characterize it. Although it is a life-threatening disease caused by a systemic inflammatory reaction, it is difficult to treat because treatment options are limited, and indications may be limited by the patient's background comorbidities, such as cancer or active inflammatory disease. In this case, the patient had a markedly elevated inflammatory response with a white blood cell count of 16,610/μL and a C-reactive protein (CRP) of 31.8 mg/dL. In addition, urinary L-FABP was also elevated at 57.5 μg/gCre for AKI with sCre 2.43 mg/dL, which was expected to increase prognostic risk [4]. As shown below, the patient was also severely ill, with a severity score of 15 points. Therefore, we judged that prompt therapeutic intervention was necessary.

The pathogenesis of psoriasis involves various factors in the genetic landscape, and a strong correlation with HLA-Cw6 has been reported [5]. Various dendritic cells, lymphocytes, and cytokines are intricately involved in the histology of psoriatic lesions, and TNF-α, IL-23, and IL-17 are thought to play crucial roles [6]. Psoriasis is a chronic inflammatory skin disease, and several new drugs targeting the IL-23/IL-17A pathway have recently been approved and are undergoing clinical development. In the mid-2000s, IL-23 was observed to induce the production of IL-17 by activated T lymphocytes (later named Th17 cells) [7, 8]. The involvement of IL-23 in psoriasis is supported by its ability to induce psoriasis-like characteristics in a preclinical model following intradermal administration [9]. This phenotype is associated with the infiltration of IL-22-and IL-17A-producing T cells [10]. Therefore, Th17 cells have been extensively studied, and IL-17A, a characteristic cytokine expressed on neutrophils, has been identified as an important causative factor of psoriasis [6, 11].

SEC is a fully human monoclonal IgG1 antibody that targets IL-17A. SEC is characterized by (1) several indications, (2) the rapid onset of therapeutic effects, (3) long-lasting therapeutic effects, (4) low economic burden, (5) easy dose reduction, and (6) low risk of interstitial pneumonia. SEC is the first-line treatment for PV and PsA due to its excellent efficacy, safety, and economic efficiency. Furthermore, it can also be used in elderly patients with psoriasis as dose reduction is easy. The initial dose is 300 mg, followed by five subcutaneous doses at 1, 2, 3, and 4 weeks and every four weeks thereafter. For patients weighing $\leq$ 60 kg, 150 mg doses should be considered. In clinical trials conducted overseas, the therapeutic effect of 300 mg SEC on psoriatic rashes was 81.6% for the Psoriasis Area and Severity Index (PASI) 75 remission and 59.2% for the PASI 90 remission at week 12 [12]. In a Japanese clinical trial for psoriasis, PASI 75 and PASI 90 were achieved in 82.8% and 92.1% of the patients, respectively, at week 12 [13].

GMA is an extracorporeal therapy that eradicates neutrophils, macrophages, and monocytes that accumulate in inflammatory tissues, contribute to lesion formation and regulate cellular functions. Granulocytes and monocytes are adsorbed onto the Adacolumn carrier via the IgG-FcγR and iC3b-CR3 (Mac-1) ligand-receptor interactions as granulocytes and monocytes recognize the page as a foreign entity and capture it [14]. Passage cells are contact-stimulated and return to the organisms with modified functions. Moreover, superficial and deep veins may be used for access as the blood flow in the treatment is low. Safer puncture under echo guidance in GMA has also been applied previously [15]. In the present case, a blood access catheter was inserted as the patient had severe skin symptoms in the elbow fossa and few signs around the neck. Multicenter trials have been conducted to confirm the efficacy and safety of GMA [16], but no randomized controlled trials have been conducted. Due to the limited number of patients, the large number of severe cases, and nature of extracorporeal circulation therapy, it is difficult to conduct a double-blind, placebo-controlled study; therefore, the accumulation of case reports is expected. A previous report described a mechanism of selective adsorption and removal of activated pathological granulocytes and monocytes [17], which is expected to be beneficial based on the response mechanism. Many IL-17 products, including SEC, are administered weekly for the first month in order to reach the therapeutic plasma concentrations, so as to allow them to work immediately; however, it takes the drug an average of 6 days [18] to reach peak serum concentrations, thus it is unlikely that its full efficacy is realized within the first 2–3 days of treatment [19]. During an acute exacerbation of GPP, there is often no time window of a week because of the rapid progression of systemic inflammation due to cytokine storm. Our patient's case was a particularly severe one, with underlying conditions such as poorly controlled DM and AKI on CKD, and the rapid systemic fluid overload could threaten the circulatory system. Because SEC alone would leave the patient exposed to a life-threatening condition before it was fully effective, GMA was used in combination with SEC in this case. Due to its mechanical properties, GMA should be promptly effective immediately after administration and is expected to confer an immediate therapeutic benefit. In the present case, GMA was remarkably effective immediately after treatment. GMA is also easy to introduce because many of its side effects are minor and are not limited by patient background conditions, such as comorbidities or age.

Recently, Yoshikawa et al. reported a case of impetigo herpetiformis, a pregnancy-associated variant of GPP that was refractory to treatment despite various therapies and GMA, in which remission was induced after the introduction of SEC [20].

In conclusion, GMA can eliminate activated leukocytes, and the early introduction of IL-17 monoclonal antibody combined with GMA may allow disease suppression in patients with severe GPP, thus avoiding the progression to multiorgan failure. Further studies may verify the effects of IL-17 monoclonal antibodies and GMA on severe GPP.

Abbreviations

GPP: Generalized pustular psoriasis; GMA: Granulocyte/monocyte adsorption apheresis; CyA: Cyclosporine; PV: Psoriasis vulgaris; SEC: Secukinumab; IFX: Infliximab; ADA: Adalimumab; UST: Ustekinumab; IXE: Ixekizumab; BRO: Brodalumab; PsA: Psoriatic arthritis; EP: Erythrodermic psoriasis; PASI: Psoriasis Area and Severity Index.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-022-00439-y.

Additional file 1: Figure S1. Based on the Japanese guidelines for the management and treatment of generalized pustular psoriasis [2], the patient was classified as severe (11–17), with a skin severity score of 8 (0–9) and a clinical and laboratory severity score of 7 (0–8), for a total score of 15

Acknowledgments

Not applicable.

Author contributions

KS and DK performed GMA and prepared the manuscript; AK and TT treated psoriasis from a dermatological point of view; NN and MS, YK, KT, TN, YY, MS, TF, and HT performed GMA. All have read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This case study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Additional informed consent was obtained from the patients for whom identifying information was included in this article.

Competing interests

The authors declare that they have no competing interests.

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